CONTROL OF SKIN AND SKELETAL MUSCLE BLOOD VESSELS DURING HEMORRHAGE

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ABSTRACT

CONTROL OF SKIN AND SKELETAL MUSCLE
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By

John Edward Hall

A combined gravimetric and segmental resistance technique was used to study the contributions of passive vascular collapse, sympathetic nerve activity, and circulating hormones to hemorrhage-induced changes in net transcapillary fluid movement, vascular capacitance, and large and small vessel resistance in the forelegs of 55 dogs anesthetized with sodium pentobarbital.

In one series of experiments (Series I; n=16), the forelimb nerves were left intact and arterial perfusion pressure was reduced in steps to 100, 75, 50, and 35 mm Hg by compression of the brachial artery with a screw clamp. The local hypotension produced by clamping elicited slight increases in vascular resistances which were significant ($P < 0.05$) only at brachial artery pressures (P_{BA}) of 75 mm Hg and below in skeletal muscle and at 50 mm Hg and below in skin. Local hypotension caused a slow phase limb weight loss (attributed to a net reabsorption of extravascular fluid) which reached a maximum of 0.15 ± 0.02 g/min at a

P_{BA} of 50 mm Hg. The clamp was removed and after forelimb arterial and venous pressures and blood flows had returned to pre-clamp control values, P_{BA} was reduced in steps to 100, 75, 50, and 35 mm Hg by rapid bleeding from a carotid artery into a pressurized reservoir. Hemorrhagic hypotension caused marked and progressive increases in forelimb total and segmental vascular resistances along with slow phase decreases in limb weight. At each of the pressure reductions produced by hemorrhage, increases in total and all segmental resistances in skin and skeletal muscle, as well as the slow phase decreases in forelimb weight, were significantly greater ($P < 0.05$) than those observed at corresponding P_{BA}'s during local hypotension. Fast phase changes in forelimb weight, attributed primarily to reductions in intravascular volume, were consistently greater during hemorrhagic hypotension than during corresponding amounts of local hypotension. The forelimb resistance and weight data indicate that the decreased vascular capacity and extravascular fluid reabsorption observed during hemorrhage are not primarily the result of passive vessel collapse, but are largely due to active constriction of forelimb vessels. The resistance data indicate that most of the hemorrhage-induced constriction in all forelimb vascular segments, including the large veins, can also be attributed to active smooth

muscle contraction rather than to passive vascular collapse subsequent to reductions in transmural pressure.

In Series II (17 dogs), the forelimb nerves were severed, and arterial perfusion pressure was reduced by clamping the brachial artery and by hemorrhage according to the protocol described for Series I. Clamping the brachial artery produced slight increases in forelimb vascular resistances, whereas hemorrhage produced a much more pronounced constriction in all skin and muscle vascular segments. Except in the large skin arteries, the hemorrhage-induced constriction of denervated forelimb vascular segments was not substantially less than that of innervated segments. Slow phase limb weight losses during hemorrhage were not significantly different in innervated and denervated forelimbs. These data suggest that circulating vasoconstrictors, rather than sympathetic nerves, mediate most of the increased vascular resistance and extravascular fluid reabsorption in skin and skeletal muscle during rapid, severe hemorrhage.

In Series III, the forelimbs of 5 recipient dogs were pump-perfused with carotid arterial blood from 5 donor dogs. Forelimb perfusion pressure was controlled by a servosystem which continuously adjusted the pump flow rate. After a 20-30 min control period, the recipient dog was rapidly

bled so that its mean systemic arterial pressure was reduced in steps to 100, 75, 50, and 35 mm Hg. After each hemorrhage, the set-point of the servosystem was altered so that brachial artery pressure matched the recipient dog's systemic arterial pressure. Bleeding the recipient dog elicited relatively small but significant increases ($P < 0.05$) in skin and skeletal muscle vascular resistances. At a brachial artery pressure of 35 mm Hg, skin and muscle total resistance increased only 4.2 and 3.4 fold, respectively.

The shed blood was reinfused, the forelimb nerves were severed, and intravascular pressures and venous outflows allowed to stabilize. The donor dog was then rapidly bled and forelimb perfusion pressure of the recipient dog reduced according to the protocol described for bleeding the recipient dog. Bleeding the donor dog elicited large increases in vascular resistances in the forelimbs of the recipient dogs. Total vascular resistance in skin and skeletal muscle increased 12.0 and 10.6 fold respectively at a brachial artery pressure of 35 mm Hg. These data support the findings in Series I and II; i.e., that most of the increased skin and muscle vascular resistance observed during rapid, severe hemorrhage is mediated by circulating vasoconstrictors rather than by sympathetic nerves.

John Edward Hall

To determine whether the relative importance of neural and humoral control of the forelimb vasculature is influenced by the bleeding rate, 17 dogs (8 with innervated and 9 with denervated forelimbs; Series IV) were bled 0.41 ml/kg body weight per minute for 60 minutes, and changes in forelimb vascular resistances determined every 2 minutes during the bleeding period. After 60 minutes of bleeding, total skin vascular resistance increased 7.6 $\pm$ 2.8 fold in innervated limbs, but only 1.9 $\pm$ 0.3 fold in denervated limbs. In the muscle vasculature, denervation attenuated the constrictor response to hemorrhage; but, total muscle vascular resistance in denervated forelimbs still increased 3.0 $\pm$ 0.6 fold after 60 minutes of bleeding. These data indicate that during slow, sustained hemorrhage, the resistance response of the skin vasculature is almost entirely neurogenically mediated, whereas in skeletal muscle, both circulating vasoconstrictors and sympathetic nerves contribute to the increased vascular resistance.

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John Edward Hall

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To Becky and My Parents

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TABLE OF CONTENTS

TABLE OF CONTENTS--Continued Page

TABLE OF CONTENTS--Continued

LIST OF TABLES

LIST OF TABLES--Continued

LIST OF TABLES--Continued

LIST OF TABLES--Continued

LIST OF FIGURES

LIST OF FIGURES--Continued

INTRODUCTION

Hemorrhage initiates direct and reflexly mediated changes in the cardiovascular system. Some of these changes tend to restore blood volume while others redistribute cardiac output helping to maintain perfusion in the coronary and cerebral circulations at the expense of that in tissues more capable of withstanding temporary oxygen and nutrient deficits. Restoration of the effective blood volume (ratio of blood volume to vascular capacity) following hemorrhage is accomplished partly by absorption of extravascular fluid into the circulation (6,16,31,75,90,98), by decreased renal excretion of salt and water (53,59,60, 119,120), and by reduction of the intravascular capacity (31,41,69,89). Cardiac output is redistributed as a result of vasoconstriction in some tissues, especially skin, skeletal muscle, adipose, splanchnic, and renal, while in myocardial and cerebral tissues, little or no constriction occurs (31,48,55). The increase in total vascular resistance resulting from systemic vasoconstriction helps to maintain arterial pressure and perfusion of the myocardium and brain, which are not capable of withstanding prolonged oxygen and nutrient deficits.

Because hemorrhage-induced constriction is most intense in precapillary vessels (31,75,89,98), the pre- to postcapillary resistance ratio increases, tending to lower capillary hydrostatic pressure, to promote absorption of extravascular fluid, and to help restore plasma volume. The venous constriction observed during hemorrhage decreases intravascular capacity and thereby helps to maintain venous return and cardiac output despite the reduced blood volume (53,69).

Skin and skeletal muscle are important sites for some of the initial compensatory responses to bleeding because of their large vasoconstrictor response (21,22,66,89,115), and because they comprise a large proportion of the total body mass. In man, skeletal muscle and skin make up approximately 50 and 6 percent, respectively, of the total body mass (121) and together, during resting conditions, receive approximately 25 percent of the total cardiac output (53). Because of their potential compensatory importance, responses of the skin and skeletal muscle vasculature to hemorrhage have been studied by many investigators (21, 22,66,75,89,98,115).

Although the initial vasoconstriction, reduction in intravascular capacity, and reabsorption of extravascular fluid in skin and skeletal muscle during hemorrhage are well documented (21,22,31,89,115), there is considerable disagreement about the mechanisms by which these changes occur.

Some investigators (41,75,87,108) suggest that the venous constriction, and the consequent reduction in intravascular volume observed during hemorrhage, is due primarily to passive collapse of veins subsequent to a fall in transmural pressure. Others (76,89,98) suggest that venous constriction and intravascular fluid mobilization are due largely to active smooth muscle contraction.

There are also conflicting reports about the relative importance of sympathetic nerves and circulating vasoconstrictors in mediating the active portion of the increased vascular resistance in skin and skeletal muscle during hypovolemia. According to Bond et al. (21,22), circulating catecholamines are the primary mediators of the hemorrhage-induced vasoconstriction in skin, whereas both sympathetic nerves and circulating catecholamines mediate the increased vascular resistance in skeletal muscle. However, several other investigators (89,93,95,96,98) have reported that sympathetic nerves are the primary mediators of the resistance response to hemorrhage in both skin and skeletal muscle. These disparate findings may be related to differences in experimental design. Most investigators have standardized hemorrhages either according to the amount of hypotension produced (21,22,75), or the total volume of blood removed (89,115). In some cases (87) the rate of blood loss has been controlled, but few investigators have examined the effect of different bleeding rates on skin and

muscle vascular control. The present study was designed to examine systematically the relative contributions of neural, humoral, and passive factors to the compensatory vasoconstriction, reduction in intravascular capacity, and reabsorption of extravascular fluid which occur in skin and skeletal muscle during hemorrhage.

LITERATURE REVIEW

I. Control of Vascular Resistance During Hemorrhage

A. General Considerations

According to the law of Pouiseuille, the determinants of resistance to fluid flow in cylindrical tubes are:

$$R = \frac{8\ nl}{\pi\ r^4} \qquad \text{eq. 1}$$

where: R = resistance to fluid flow

n = fluid viscosity

l = tube length

$\frac{8}{\pi}$ = constant of proportionality

r = tube radius

Although this relationship applies to Newtonian fluids (in which the ratio of shear stress to shear strain is constant) flowing in cylindrical tubes, it has been used extensively in modeling the circulation and analyzing the factors which contribute to the control of vascular resistance during hemorrhage. Physiologically, the most important factor in equation 1 influencing vascular resistance is blood vessel radius. The radii of blood vessels can be altered by contraction and relaxation of circularly arranged vascular smooth muscle, which in turn is influenced by autonomic

nerves, circulating vasoactive chemicals, local vasodilator metabolites, and physical factors such as transmural pressure (intraluminal pressure-tissue pressure). An "active" change in vascular radius is mediated through an alteration in the contractile state of vascular smooth muscle; a "passive" change in radius is any change not mediated through alterations in the contractile state of vascular smooth muscle (72). During hemorrhage, both active and passive constriction contribute to the increased vascular resistance in skin and skeletal muscle (72). Since resistance is inversely proportional to the fourth power of the radius (equation 1), small decreases in blood vessel radius will produce marked increases in vascular resistance.

Changes in blood viscosity (equation 1) may also contribute slightly to elevations in skin and skeletal muscle vascular resistance during hemorrhage. Early in hemorrhage, blood viscosity may increase slightly since flow velocity is decreased, and in some species, splenic contraction releases blood rich in red cells into the circulation resulting in a transient increase in hematocrit (31,72,110). The increase in hematocrit is not prolonged since reabsorption of extravascular fluid into the circulation returns the red blood cell concentration toward normal (72,75). Consequently, increases in blood viscosity are probably of minor importance in increasing vascular resistance during hemorrhage (31,72).

The other variable in equation 1 which could influence vascular resistance during hemorrhage is blood vessel length. Since the length of blood vessels is normally constant, increases in skin and muscle vascular resistance during hemorrhage are due primarily to reductions in blood vessel radius (72). Hemorrhage could reduce vessel radius by eliciting constriction mediated through sympathetic nerves or through the release of hormones such as catecholamines, angiotensin, and vasopressin. When blood loss is severe enough to reduce transmural pressure, passive vascular constriction may also contribute to the increased resistance to blood flow, especially in veins.

B. Neural Control

Sympathetic adrenergic nerve fibers are considered by many investigators to play the dominant role in adjusting skin and muscle vascular resistance during hemorrhage (89, 93,95,96,98). Adjustments of blood flow by sympathetic constrictor fibers depends on regional nerve fiber distribution density, effector sensitivity, and variations in vasoconstrictor fiber discharge frequency (53).

Several investigators have studied the distribution of adrenergic nerve terminals in the vasculature of skin and skeletal muscle. Fuxe and Sedvall (58) found that large arteries and veins in the cat gastrocnemius and tibialis anterior muscles had sparse adrenergic innervation,

but that intramuscular small arteries, arterioles, and metarterioles were richly supplied with adrenergic nerve terminals. Angelakos et al. (11), using fluorescence histochemical techniques, found extensive adrenergic innervation in all skeletal muscle vessels. In skin, arteries, small vessels, and veins, all have an abundant adrenergic innervation (53,46).

Effector sensitivity to sympathetic nerve stimulation has been studied in several skin and muscle vascular beds. In the dog forelimb (a combined skin and skeletal muscle preparation), stimulation of nerve fibers within "physiological" frequencies (1-16 impulses/sec) produced increases in total forelimb vascular resistance due primarily to increases in skin large artery resistance, but partly due to constriction of muscle large arteries and veins, and skin large veins (3,5). However, in the skin and muscle small vessels, which provided the greatest percentage of total forelimb vascular resistance, nerve stimulation produced no consistent changes in resistance (3,5). Hammond, Davis, and Dow (78) studied resistance changes of the arterial, small vessel, and venous segments of the dog hind paw (primarily skin) during stimulation of the sciatic nerve and three of its branches (tibial, deep and superficial fibular nerves). They observed increased resistance in all vascular segments during sciatic nerve stimulation with the greatest percent increases occurring in the large artery

segment. Small vessel resistance increased only 16 percent above control values even during supermaximal voltage and frequency stimulations. Zimmerman (130) also observed large increases in skin arterial resistance but relatively minor small vessel constrictor responses during sympathetic nerve stimulation. These studies demonstrate that stimulation of sympathetic nerves elicits increases in skin and skeletal muscle vascular resistance mainly by constricting large arteries. The small vessels, which offer the largest percent of total vascular resistance, are relatively unresponsive to sympathetic nerve stimulation.

Variation of sympathetic nerve fiber discharge frequency during hemorrhagic hypotension has also been examined (18,34,61,62). Gernadt et al. (61), reported that hemorrhage increased efferent impulses in the splanchnic nerve of the cat. Corazza (34) recorded action potentials in the cervical sympathetic nerve of rats and reported an increase in frequency after hemorrhage. Beck and Dontos (18) reported increases in electrical activity of splanchnic nerves in both dogs and cats hemorrhaged to mean arterial pressures of 55 and 45 mm Hg.

Other investigators have attempted to determine indirectly changes in sympathetic impulse traffic during hemorrhage by comparing the hemodynamic responses in the skin and skeletal muscle vasculature observed during graded sympathetic nerve stimulation to those found in hemorrhage.

Lungren et al. (89) using cat hindlimb muscles cross-perfused at constant flow with blood from normovolemic donor cats, concluded that various levels of hemorrhage were associated with increases in sympathetic impulse frequency from a control value of less than 1 impulse per second to as high as 7 impulses per second. Evaluation of changes in sympathetic activity was based on comparison of reflexly mediated resistance changes during hemorrhage with those obtained by graded stimulation of hindlimb vasoconstrictor nerve fibers.

Neural control of vascular resistance during hemorrhage has also been studied by comparing the hemodynamic responses of innervated and denervated skin and skeletal muscle vascular beds. Green (63), observed that hemorrhage produced an increase in cutaneous vascular resistance which could be partially blocked by acute denervation. Rothe et al. (109), perfusing the dog gracilis muscle at constant arterial pressure, reported a rise in vascular resistance after hemorrhage which was abolished by cooling the gracilis nerve. Bond et al. (21), using a dog hindpaw preparation (primarily skin), reported that acute denervation did not attenuate the resistance response to severe bleeding, and concluded that cutaneous vasoconstriction during hemorrhage was not mediated by sympathetic nerves. In another study, using a dog hindlimb preparation (primarily muscle), Bond et al. (22) reported that denervation reduced but did not

abolish the resistance response of the muscle vasculature to hemorrhage, suggesting that both sympathetic nerves and circulating hormones mediated the vasoconstriction in muscle.

Although the resistance vessels of skin and skeletal muscle are innervated by sympathetic adrenergic fibers, most of the available data suggest that hemorrhage-induced constriction, especially in small vessels, is not mediated entirely by nerves. The small vessels, which offer the largest percentage of resting resistance and the greatest capacity to increase resistance during hemorrhage, show little response to nerve stimulation. Therefore, the large increases (10 fold) in vascular resistance during severe hemorrhage are mediated partly by circulating vasoconstrictors.

C. Humoral Control

1. Catecholamines

Activation of the sympathetic nervous system by blood loss increases release of epinephrine and norepinephrine from the adrenal medulla (45). Investigators using bioassay or fluorometric techniques demonstrated that hemorrhage resulted in elevated catecholamine concentrations in systemic (19,77) or adrenal venous blood (56,124,126).
In reviewing the data from several studies on hemorrhage in anesthetized dogs, Watts (125) reported that severe blood loss may result in a 50 fold increase in systemic venous

plasma concentration of epinephrine and a 10 fold increase in norepinephrine concentration. Similar results were found in unanesthetized dogs (125). Hall and Hodge (77) observed no increase in circulating catecholamine levels in the dog during slow hemorrhage which was not severe enough to lower mean arterial pressure. However, rapid hemorrhage which significantly reduced mean arterial pressure, resulted in marked increases in blood catecholamine concentrations. Carey (28) measured the adrenal secretory rate of epinephrine and norepinephrine in unanesthetized pigs and reported that slow, continuous hemorrhage (10 percent reduction in blood volume in 30 minutes or 30 percent reduction in 90 minutes) elicited no significant increases in adrenal vein epinephrine and norepinephrine concentrations even if bleeding was continued until mean arterial pressure was reduced to 50-60 mm Hg. However, he reported that rapid blood losses (10 percent of the total blood volume in 10 minutes or 30 percent in 30 minutes) elicited large increases in both epinephrine and norepinephrine concentrations in adrenal venous blood. He concluded that the rate of release of catecholamines from the adrenal medulla during hemorrhage depended on the rate of blood loss more than the magnitude of the blood pressure reduction produced. These data indicate that large increases in blood catecholamine concentrations can occur during rapid, severe hemorrhage, but during slow hemorrhage blood catecholamine

levels may not be significantly increased.

Several investigators have demonstrated that catecholamines are potent cutaneous and skeletal muscle vasoconstrictors (2,5,37,92,129). Abboud and Eckstein (5) reported that 1 and 2 μg injections of norepinephrine into the arterial supply of the dog forelimb produced marked increases in total skin vascular resistance due primarily to constriction of small vessels and large veins. In the muscle vasculature, norepinephrine injection increased small vessel and venous resistances, but much less so than in the skin vasculature. In another study, Abboud (2) infused norepinephrine into the dog gracilis muscle and hindpaw and confirmed his findings in the forelimb. Mellander (92) found similarities between the responses to norepinephrine and sympathetic nerve stimulation in the hindlimbs of cats (primarily skin and muscle). In Mellander's studies, the arterial and venous pressures were held constant and changes in hindlimb weight, rate of venous outflow, and protein content of the drained venous plasma were measured. Since arterial and venous pressures were held constant, and plasma protein concentrations were not measureably altered by nerve stimulation or norepinephrine infusion, changes in limb weight after flow had stabilized were assumed to be due to alterations in the pre- to postcapillary resistance ratio. He concluded from these studies that norepinephrine, as well as nerve stimulation, constricted

precapillary vessels relatively more than postcapillary vessels. These studies (2,5,92,129) indicate that catecholamines produce marked increases in skin and skeletal muscle vascular resistance in normovolemic animals. However, some investigators suggest that during hemorrhage, vascular constriction due to increased release of catecholamines from the adrenal medulla is relatively minor compared to that produced by sympathetic nerve stimulation.

Celander (29) estimated that the maximal secretion rate of catecholamines (both norepinephrine and epinephrine) from the adrenal medulla was not greater than 5 µg/kg body weight per minute. The vasoconstriction induced by intravenous infusions of norepinephrine and epinephrine at doses ranging from 0.1 to 5 µg/kg body weight per minute in these studies was always much less than that produced by sympathetic nerve stimulation within "physiological" ranges (i.e., 1-16 impulses/sec.). Celander also noted that stimulation of the nerve supply to the adrenal gland, which releases catecholamines into the systemic circulation, was much less effective in producing vasoconstriction than was stimulation, at comparable frequencies, of nerve fibers to the leg muscles. He concluded from these studies that blood vessels of skin and skeletal muscles are dominated by activity of sympathetic adrenergic fibers and that any constriction by catecholamines from the adrenal medulla is relatively insignificant.

Several investigators (53,95,98) have extrapolated Celander's observations to suggest that circulating catecholamines are not important mediators of vasoconstriction in skin and skeletal muscle during hemorrhage. However, Celander's findings may not be applicable to hypovolemic animals for the following reasons: a) Celander assumed that splanchnic nerve stimulation (up to 10 impulses/sec) produced maximum release of epinephrine and norepinephrine from the adrenal medulla. However, several studies suggest that during hemorrhage other factors such as hypoxia of the adrenal medulla, and elevated concentrations of angiotensin, vasopressin, and adrenal corticoids also contribute to an increased release of catecholamines from the adrenal medulla (31,47,77,79); b) Celander attempted to determine the effects of maximum "physiological" doses of catecholamines on skin and skeletal muscle vascular resistance by infusing the catecholamines intravenously in normovolemic animals. However, vasopressin, angiotensin, and adrenal corticoids which are all released during hypovolemia (36,77, 107,119), not only stimulate the release of catecholamines, but also potentiate their effects on vascular smooth muscle contraction (4,8,113,114,131). Consequently, during hemorrhage, when vasopressin, angiotensin, and adrenal corticoid blood concentrations are elevated, the effects of catecholamines on vascular smooth muscle contraction may be greater than in a normovolemic, normotensive animal; c) Intravenous

infusion of catecholamines in normovolemic animals may have produced reflex effects (i.e., an increased blood pressure causing reductions in the release of circulating vasoconstrictors such as angiotensin or vasopressin) which may have partially masked the direct effects of the infused catecholamines on the skin and muscle vasculature.

Because the concentrations of circulating catecholamines in hypovolemic animals may not be the same as those produced by splanchnic nerve stimulation, and because the effects of catecholamines on vascular smooth muscle contractions may differ in normovolemic and hypovolemic animals, it is hazardous to conclude from Celander's study that circulating catecholamines do not affect vascular resistance during hemorrhage. The studies of Bond et al. (21) suggest that during hemorrhage, circulating catecholamines are the primary mediators of the resistance response in skin vessels, and contribute significantly to the vasoconstriction in skeletal muscle.

2. Angiotensin

Elevated plasma concentrations of angiotensin may also contribute to increased vascular resistance in skin and skeletal muscle during hemorrhage. Several investigators have shown that the blood concentration of angiotensin rises during hemorrhage (24,32,77). The data of Claybaugh and Share (32) and Brown (24) indicate that renin release, and presumably angiotensin formation, is related to the rate of

blood loss; slow rates of hemorrhage did not increase plasma renin concentrations significantly, but rapid blood losses increased plasma renin concentrations markedly.

Increased plasma concentrations of angiotensin exert a direct vasoconstrictor effect on skin and skeletal muscle blood vessels (2,51,70,129). Experiments on cat hindlimbs (51) and dog forelimbs (2,70) indicated that angiotensin infusion produces a marked constriction in precapillary resistance vessels. Zimmerman (129) and Abboud (2) reported that angiotensin's vasoconstrictor action was augmented at high sympathetic tone.

In addition to its direct effects on skin and muscle vascular resistance, angiotensin exerts indirect effects on vascular tone through adrenergic mechanisms. Feldberg and Lewis (47) demonstrated that angiotensin stimulates release of catecholamines from the adrenal medulla. Angiotensin also increases release of norepinephrine from peripheral nerve endings, stimulates discharge of central vasomotor neurons, and interacts with catecholamines at alpha receptors to augment contraction of vascular smooth muscle (131).

The significance of angiotensin in mediating increases in vascular resistance in skin and skeletal muscle during hemorrhage has not been thoroughly evaluated. Although McNeill *et al.* (91) reported that angiotensin is an important mediator of intestinal vasoconstriction during hemorrhage,

some investigators (72,73,95) conclude that the rising concentrations of angiotensin are not sufficient to cause important direct effects on vascular resistance. However, angiotensin's indirect effects on vascular resistance through adrenergic mechanisms may contribute significantly to the vasoconstriction observed during hemorrhage.

3. Vasopressin

Vasopressin, a potent skin and skeletal muscle vasoconstrictor (73,95), is released from the posterior pituitary during hemorrhage (119). Because vasopressin exerts antidiuretic effects at plasma concentrations well below those required for vascular changes, some investigators suggest that vasopressin is most important as a regulator of water reabsorption in the renal tubules and does not contribute significantly to the regulation of vascular resistance (53,95). However, Rocha e Silva and Rosenberg (107) reported that infusions of vasopressin, which reproduced plasma concentrations observed during hemorrhage, caused pressor responses. In a recent study, Schmid et al. (112) reported that intravenous infusions of 1-2 μU vasopressin/kg per minute, which produced plasma concentrations below those reported during hemorrhage, elicited a significant vasoconstriction in dog skeletal muscle. The increased vascular resistance was attributed to a direct effect of vasopressin on vascular smooth muscle since hexamethonium bromide, which blocks transmission in autonomic

ganglia, was administered. Other investigators (2,71) have demonstrated that intra-arterial infusions of vasopressin constrict precapillary resistance vessels in skin and skeletal muscle.

The role of vasopressin in the regulation of skin and skeletal muscle vascular resistance during hemorrhage has not been investigated extensively. In a study using the dog forelimb, Haddy et al. (75) reported that the constrictor response to hemorrhage was abolished by a combination of carotid sinus procainization, vagotomy, adrenalectomy, and bilateral nephrectomy. The investigators assumed that these four procedures blocked adrenergic and angiotensin constrictor mechanisms but did not reduce the release of vasopressin during hemorrhage. Therefore, they concluded that the vasopressin released during hemorrhage was not sufficient to constrict forelimb vessels. However, Rocha e Silva and Rosenberg (107) reported that arterial baroreceptors play a very important role in the hemorrhage-induced release of vasopressin. Consequently, in Haddy et al's. study carotid sinus procainization and vagotomy may have inhibited vasopressin secretion during hemorrhage.

D. Passive Responses

Sympathetic nerve stimulation, catecholamines, angiotensin, and vasopressin all constrict the skin and skeletal muscle vasculature through active changes in blood vessel radius (changes due to contraction of vascular smooth muscle).

However, when blood loss is severe enough to lower arterial and venous pressures, passive constriction (due to elastic recoil of blood vessels subsequent to a decreased transmural pressure) may also contribute to the increased vascular resistance in skin and skeletal muscle.

Precapillary vessels, which provide most of the total skin and skeletal muscle vascular resistance, show only small changes in resistance when perfusion pressure is reduced (54,94,95). This response is due in part to local vasodilatory mechanisms which relax arterioles when perfusion pressure is reduced (74,95), but occurs partly because precapillary resistance vessels have a relatively large wall thickness to lumen diameter ratio (27), and therefore can withstand reductions in transmural pressure without collapsing.

The large veins have a relatively low wall thickness to lumen diameter ratio and some investigators have proposed that the venous constriction observed during hemorrhage results primarily from passive vascular collapse subsequent to a reduced transmural pressure (75,87). Other investigators (76,89) have concluded that active constriction, rather than passive vascular collapse, accounts for most of the increased venous resistance during hemorrhage (see section II-D for a discussion of active vs. passive changes in venous resistance during hemorrhage). Regardless of the relative importance of active and passive venous constriction

during hemorrhage, passive collapse probably contributes only slightly to the increased total skin and skeletal muscle vascular resistance which accompanies hemorrhage, since large veins offer a small fraction of the total resistance (1).

II. Control of Vascular Capacitance During Hemorrhage

A. General Considerations

Decreased vascular capacitance helps to compensate for hemorrhage by transiently displacing blood from vessels and thereby providing a momentarily increased venous return. The new steady state decrease in capacitance results in a smaller vascular volume and a shorter mean transit time for blood flow from the left to the right heart. This decreased transit time helps to maintain venous return and cardiac output despite a decreased blood volume.

Veins are especially important in changing vascular capacitance because they contain most (60-80 percent) of the total blood volume (7,128). Reductions in venous capacitance during hemorrhage could result from passive collapse of veins subsequent to decreases in venous transmural pressure or from active contraction of venous smooth muscle. Active venoconstriction during hemorrhage could be mediated by increased sympathetic adrenergic nerve stimulation and/or increased concentrations of blood-borne vasoconstrictors

such as catecholamines, angiotensin, or vasopressin. While there is general agreement that vascular capacitance in skin and skeletal muscle is reduced during hemorrhage, there is disagreement about the relative importance of neural, humoral, and passive venoconstriction in mediating these capacitance changes.

B. Neural Control

Large veins in skin and skeletal muscle are innervated by sympathetic adrenergic fibers (3,46,58), and stimulation of these fibers elicits active venoconstriction (3,50,78, 130). Mellander (92), using graded sympathetic nerve stimulation, observed marked increases in resistance and decreases in capacitance of skin and skeletal muscle veins. When sympathetic nerves were stimulated during a period of complete arterial occlusion, a decrease in tissue volume was observed. Since arterial inflow was stopped, the reduction in tissue volume could not have been due to passive collapse of veins subsequent to arteriolar constriction (which would decrease venous inflow), but was attributed to active constriction of capacitance vessels. Mellander estimated that at "basal vascular tone" (resting contractile state of vascular smooth muscle when all known extrinsic excitatory influences are removed) up to one-third of the blood in a skin and skeletal muscle preparation could be mobilized as a result of sympathetically mediated venous constriction.

Other investigators have studied venomotor reactions to nerve stimulation by monitoring pressure changes in occluded veins. After the vein has been occluded and the venous pressure has stabilized, any change in venous pressure is presumed to be due to active changes in venous tone as long as extravascular compression due to skeletal muscle contraction is eliminated by a neuromuscular blocking agent. Browse et al. (26), using the venous occlusion technique, found that sympathetic nerve stimulation produced active constriction of veins in the dog hindlimb (primarily skin and skeletal muscle). Browse et al. (25), using this same technique, also reported that carotid sinus hypotension produced reflexly mediated decreases in venous capacitance.

Although most investigators agree that sympathetic nerve stimulation can elicit significant increases in venous resistance and decreases in capacitance, there is disagreement about the importance of neurogenically mediated capacitance changes during hemorrhage. Lesh and Rothe (87) studied reflex venoconstrictor responses in dog gracilis muscle during hemorrhage and during local hypotension produced by mechanically reducing arterial inflow. Since the initial rapid phase of muscle weight loss (attributed primarily to reduction in intravascular capacity) was not significantly greater during hemorrhage than during local hypotension, they concluded that active venous constriction

accounts for a negligible fraction of the reduced venous capacitance observed during hemorrhage. Instead, Lesh and Rothe attributed most of the decreased venous capacitance to elastic recoil of veins subsequent to a reduced transmural pressure. However, they noted that when blood flow was held constant, sympathetic nerve stimulation produced a decrease in mean transit time ($\bar{T}$) of a tracer dye (indocyanine green). The relationship between $\bar{T}$, blood flow (F), and blood volume (V) in a vascular bed is expressed as:

$$V = F \times \bar{T} \qquad \text{eq. 2}$$

In Lesh and Rothe's study, the observation that nerve stimulation decreased $\bar{T}$ with F held constant implies that vascular volume was reduced. They suggested that $\bar{T}$ may have been reduced because nerve stimulation contracted precapillary sphincters causing "functional shunting" of blood (i.e., a high proportion of blood flowing through relatively short, direct channels from the arterial to the venous side). Although non-exchange shunt vessels have not been observed in skeletal muscle (17), the concept of "functional shunting" is supported by Renkin and Rosell's (105) observation that nerve stimulation decreased the extraction of ^{86}Rb during constant flow perfusion. But even if short, non-exchange shunt vessels do exist, there is no evidence in Lesh and Rothe's study that the reduced mean transit time which they

observed during nerve stimulation was due to shunting of blood rather than to decreased vascular capacity.

C. Humoral Control

Active constriction of veins due to increased concentrations of circulating vasoconstrictors such as norepinephrine, epinephrine, angiotensin, and vasopressin may contribute to decreases in vascular capacitance during hemorrhage. Norepinephrine and epinephrine have been shown to constrict veins in the human forearm (17), dog forelimb (5), dog hindpaw (130) and dog gracilis muscle (87). Tissue volume changes, measured with plethysmographic (92) or gravimetric techniques (118) indicate that catecholamine infusions or injections produced decreases in venous volume. Shadle et al. (118) using a dog hindlimb preparation placed in a plethysmograph and perfused at constant arterial inflow, observed an increased perfusion pressure (indicating increased resistance to blood flow), a transient decrease in venous outflow, and a transient increase in limb weight during norepinephrine infusion. They attributed the initial increase in weight to distention of arteries proximal to the site of constriction. Eventually as the rising perfusion pressure overcame the increased resistance to flow, venous outflow increased above arterial inflow and limb weight decreased rapidly. They concluded that the rapid decrease in limb weight was due to translocation of blood centrally

by active constriction of veins. Because only small changes in blood concentrations of plasma-tag T-1824 and erythrocyte-tag ^{32}P occurred as limb weight was reduced, only a small part of the change in limb weight was attributed to net reabsorption of interstitial fluid. Mellander (92) noted decreases in flow and vascular volume in the cat hindleg during norepinephrine infusion and concluded that both resistance and capacitance vessels were actively constricted. Intra-arterial infusions of epinephrine resulted in transient increases in venous outflow, simultaneously with a decreased limb volume, suggesting a reduction in vascular capacitance.

Although a potent constrictor of precapillary vessels, angiotensin is reported to exert minimal influence on post-capillary vessels (1,2,51,70). Folkow et al. (51) compared the effects of angiotensin and norepinephrine on the cat hindlimb when infused intra-arterially in concentrations that produced equal increases in vascular resistance, and noted that norepinephrine produced a marked decrease in tissue volume but angiotensin produced only a small decrease in tissue volume. These observations suggested that angiotensin elicited only small increases in venous resistance and hence only small decreases in vascular capacity. Abboud (2), using dog forelimb and hindpaw preparations, also noted that angiotensin produced increases in total skin and muscle vascular resistance, but did not appreciably constrict venous vessels.

Although many investigators have concluded that angiotensin does not exert significant direct effects on venous capacitance, it is possible that indirect effects of angiotensin on venous capacitance and resistance may be important during hemorrhage. Angiotensin not only stimulates the release of norepinephrine from the adrenal medulla and adrenergic nerve terminal, but is also reported to interact with catecholamines at α receptors to augment contraction of vascular smooth muscle (130). Consequently, the contribution of angiotensin to active changes in vascular capacitance during hemorrhage can not be determined simply by perfusing vascular beds of normovolemic animals with concentrations of angiotensin known to occur during hemorrhage.

Vasopressin, like angiotensin, constricts precapillary resistance vessels but exerts minimal effects on postcapillary capacitance vessels (2,20,73,95). Haddy et al. (70,71) reported that vasopressin infusions produced an increased total forelimb vascular resistance, but did not increase venous resistance. Abboud (2) found similar results in the dog forelimb and hindpaw. However, injections of vasopressin into a small digital vein caused a marked increase in digital vein pressure, suggesting that vasopressin in high concentrations will constrict veins (39).

Although these studies suggest that the direct effects of vasopressin on vascular capacitance during hemorrhage are minimal, vasopressin's indirect effects through its

interaction with other vasoconstrictors at smooth muscle receptor sites have not been investigated thoroughly. Vasopressin may contribute to decreases in vascular capacity during hemorrhage via a potentiation of the venoconstriction produced by catecholamines.

Powell and Du Charme (103) recently presented evidence that a non-angiotensin pressor material released from the kidney contributed significantly to the decreased total vascular capacity which accompanied hemorrhagic hypotension. In an earlier study, Du Charme and Beck (42) studied capacitance responses of the whole circulatory system by observing translocations of blood between the vascular system and an extracoporeal reservoir and found that the potential of the renal pressor system to reduce total vascular capacity was approximately 60 percent of the potential of the sympathetic nervous system. Although these investigators did not identify the pressor agent or the specific site(s) of decreased vascular capacity, it is possible that this pressor agent decreases vascular capacity in skin and skeletal muscle during hemorrhage.

D. Passive Responses

Active constriction of veins during hemorrhage may also be accompanied by passive expulsion of blood whenever venous transmural pressure is reduced. Venous transmural pressure could be reduced during hemorrhage by a fall in arterial

blood pressure and consequently a reduced venous inflow even if no vasomotor adjustments occurred. Active precapillary constriction further reduces venous inflow and hence venous transmural pressure.

The magnitude of passive adjustments of venous volume apparently varies considerably depending on the prevailing venous transmural pressure (99), since the distensibility of veins varies greatly with the venous pressure (7,27). At low pressures, even a small decrease in pressure is followed by a marked decrease in volume, as indicated by the convexity of the venous pressure-volume curve towards the volume axis (i.e., the distensibility of large veins is very high at low venous pressures). At high venous pressures, the veins contain a large blood volume and are distended (7,27). Öberg (99) reports that the volume of distended veins is little affected by moderate changes in transmural pressure (i.e., the distensibility of veins is low when transmural pressures are high). Consequently, during hemorrhage, the relative importance of active and passive changes in venous capacitance should vary depending upon the prevailing venous transmural pressure.

Lungren et al. (89) measured changes in regional blood volume in cat hindlimbs with a plethysmograph during hemorrhage and when blood flow was mechanically reduced to the levels observed during hemorrhage. They deduced that only 5-10 percent of the total regional blood volume was passively

expelled during moderate hemorrhage (15-20 percent of the total blood volume) while active constriction mobilized 20-25 percent of the regional blood volume. Although these data differ from those reported by Lesh and Rothe (see section II-B), who suggested that passive collapse accounted for most of the reduced vascular capacity during hemorrhage, they indicate that a small but significant reduction in vascular capacity occurs due to passive vascular collapse.

III. Transcapillary Fluid Movement During Hemorrhage

A. General Considerations

Many investigators have demonstrated that hemorrhage is accompanied by a redistribution of the extracellular fluid, leading to a compensatory increase in plasma volume at the expense of the interstitial fluid volume (6,15,16, 40). The fluid which enters the microcirculation from the tissue is largely protein free (30,38,122), and the degree and rate of entry appears to depend on the severity of the blood loss (31). Adolph et al. (6) found that dogs subjected to a 20-35 ml/kg body weight blood loss replaced 35 percent of the plasma volume deficit within 20 minutes. Hemorrhage has also been observed to cause hemodilution in man (88), cats (68), and rats (102). These studies (6,16, 30,40) indicate that a considerable amount of fluid can be mobilized rapidly from extravascular sites to aid in the

restoration of plasma volume following hemorrhage. However, the complete restoration of plasma volume requires several days, and involves reduction of renal salt and water excretion concurrently with an increased salt and water intake (59,60,119,120).

The principle factors which alter the distribution of fluid between the intra- and extravascular compartments during hemorrhage were proposed by Starling (123) as follows: the direction and rate of fluid transfer between plasma and the tissue spaces depends on the hydrostatic pressure on each side of the capillary wall, on the protein osmotic pressures of plasma and tissue fluid, and on the filtering properties of the capillary membrane. Experimental support for this hypothesis was obtained by Landis (84) for frog mesenteric capillaries and by Pappenheimer and Soto-Rivera (101) for capillaries in dog skeletal muscle. The following equation has been used to express Starling's hypothesis (85):

$$F = K\ [(P_c - P_t) - (\pi_p - \pi_t)] \qquad \text{eq. 3}$$

where:

F = rate of transcapillary fluid movement (ml/min per 100 gm tissue weight; a positive number indicates fluid filtration out of the capillaries, whereas a negative number indicates fluid reabsorption into the capillaries.

K = a coefficient for capillary filtration which represents the product of total surface area and permeability per unit surface area to the filtered fluid (ml/min per 100 gm tissue weight) x $(\text{mm Hg})^{-1}$)

P_c = capillary hydrostatic pressure (mm Hg)

P_t = tissue hydrostatic pressure (mm Hg)

π_p = plasma colloid osmotic pressure (mm Hg)

π_t = tissue fluid colloid osmotic pressure (mm Hg)

In skin and skeletal muscle, there is normally a slight net outward movement of fluid, which is returned to the circulation via the lymphatic system (53). During hemorrhage, this balance is upset, and a net reabsorption of fluid from the tissues into the microcirculation occurs. This net reabsorption could occur through several mechanisms. Reflex vasomotor adjustments could affect directly or indirectly all of the variables in equation 3, but the most direct effects are probably on capillary hydrostatic pressure (P_c), which according to Pappenheimer and Soto-Rivera (101), can be expressed as:

$$P_c = \frac{(R_v/R_a)P_a + P_v}{(R_v/R_a) + 1} \qquad \text{eq. 4}$$

where:

R_a = precapillary vascular resistance

R_v = postcapillary vascular resistance

P_a = arterial pressure

P_v = venous pressure

Hemorrhage tends to lower P_a and P_v and hence P_c, facilitating fluid transfer from the tissues into the microcirculation. Reflex alterations in the distribution of pre- and postcapillary resistance also occur during hemorrhage

due to differential effects of adrenergic nerve stimulation, circulating vasoconstrictors, and changes in transmural pressure on pre- and postcapillary vessels (73,96,98). For example, an increase in the pre- to postcapillary resistance ratio would favor a net movement of fluid into the circulation.

The rate of fluid movement across the capillaries is affected not only by the hydrostatic and colloid osmotic pressure gradients, but also by the properties of the capillary membrane (expressed by coefficient K in equation 3). Both the permeability and the surface area of the vessels available for exchange will influence the rate of fluid movement produced by a given hydrostatic or osmotic pressure gradient across the capillaries. Since capillary permeability is not altered during hemorrhage (31) or even severe hypoxia (116), changes in K depend on changes in the functional capillary surface area due to opening or closure of precapillary sphincters (31,95). For example, contractions of precapillary sphincters will exclude some capillaries from participating in fluid exchange between intra- and extravascular compartments, thus reducing the functional capillary surface area.

Two different methods have been used to evaluate relative changes in capillary surface area. One involves calculating a permeability surface area (PS) product from the arteriovenous extraction fraction of radioactive potassium or

rubidium (104,105,106), or from rate of tissue washout of hydrophilic radioactive tracers (i.e., iodide or sodium) (12,13,14,86) at known flow rates. These tracers move rapidly across the capillary membrane and backflux is usually negligible, but can be corrected for if necessary. This method cannot separate the permeability or surface area terms from the PS product. The other method is based on hydrodynamic conductivity of the exchange vessels in terms of a capillary filtration coefficient (CFC). The CFC is determined by volumetric or gravimetric recording of the amount of fluid filtration into the tissues produced by an estimated increase in P_c, assuming that P_t, π_t, and π_p remain reasonably constant (52,92,98). The capillary filtration coefficient is assumed to be largely independent of blood flow rate (94) whereas PS is recognized to vary with flow rate (105). CFC like PS, reflects the product of capillary surface area and permeability and is presumed to be proportional to PS under most conditions (94,95). Since capillary permeability is unaltered in most physiological conditions, changes in PS or CFC in a given vascular bed will reflect alterations in the functional capillary surface area (94,95).

B. Neural Control

There is general agreement that stimulation of sympathetic adrenergic nerves can alter the distribution of

intra- and extravascular fluid (31,33,92,95). Adrenergic fibers innervate pre- and postcapillary vessels, and precapillary sphincters, and stimulation of these fibers has been demonstrated to alter the rate of fluid movement across the capillaries by changing both the pre- to postcapillary resistance ratio and the capillary surface area (33,92).

Mellander (92) used cat hindlimb preparations to estimate changes in pre- and postcapillary resistance and tissue volume during sympathetic nerve stimulation. The inflow and outflow pressures were held constant while changes in tissue volume and blood flow were measured continuously. Nerve stimulation produced a rapid, transient volume reduction, attributed to a decreased vascular capacitance, followed by a slower more sustained volume reduction attributed to a net reabsorption of extravascular fluid. The movement of extravascular fluid into the capillaries was attributed primarily to a fall in capillary hydrostatic pressure subsequent to an increased pre- to postcapillary resistance ratio. Mellander also measured changes in CFC and found that initially, nerve stimulation produced a reduction in CFC; with continued stimulation, CFC increased above control, presumably because precapillary sphincters relaxed. These changes could be graded by increasing the frequency of stimulation. Öberg (98) and Cobbold et al. (33) observed similar results in cat hindlimb preparations.

Renkin and Rosell (105) measured the PS product in isolated skeletal muscles of dogs and cats perfused at constant blood flow and observed that sympathetic nerve stimulation at frequencies between 1 and 20 impulses per second produced sustained reductions in the PS product and marked increases in vascular resistance. The reductions in the PS product were attributed to a reduction in the exchange surface area presumably due to closure of precapillary sphincters.

Some investigators (66,89,98,115) have observed changes in transcapillary fluid movement during hemorrhage similar to those produced by sympathetic nerve stimulation; initially the pre- to postcapillary resistance ratio increased and some investigators report that CFC also increased (89,99) producing a substantial flux of fluid into the circulation of skin and skeletal muscle. This fluid reabsorption was abolished when the vessels were acutely denervated (96), but could be demonstrated in preparations which were completely isolated from the hemorrhaged cat except through neural connections (89). Therefore, these investigators (89,96) attributed the fluid reabsorption primarily to an increased pre- to postcapillary resistance ratio which was mediated through activation of sympathetic adrenergic nerves.

When hemorrhage was severe and prolonged, a reduction in the rate of fluid reabsorption, and eventually a net filtration of fluid into skin and muscle tissues has been

reported (89,96). These results were attributed to a reduction in the pre- to postcapillary resistance ratio due to accumulation of vasodilator metabolites which allegedly caused selective dilation of precapillary vessels while postcapillary vessels remained constricted. However, Schwinghamer et al. (115) and Grega et al. (66) noted in the dog forelimb that fluid continued to move from the tissues into the blood stream during prolonged, severe hypovolemia. They concluded that if the pre- to postcapillary resistance ratio was reduced during prolonged hemorrhage, the reduction failed to increase capillary hydrostatic pressure above control because of the large reductions in arterial and venous pressures which occurred during bleeding.

Most investigators agree that sympathetic nerve stimulation of pre- and postcapillary vessels, and precapillary sphincters initially favors the reabsorption of fluid into the microcirculation of skin and skeletal muscle during hemorrhage. However, the effect of the sympathetic nervous system on the distribution of intra- and extravascular fluid during prolonged hypovolemia is controversial.

C. Humoral Control

Since catecholamines, angiotensin, vasopressin, and possibly other constrictors are released during hemorrhage and cause vascular constriction in skin and skeletal muscle, they may also produce changes in the direction and rate of

transcapillary fluid movement by altering the pre- to post-capillary resistance ratio and/or functional capillary surface area.

The effect of norepinephrine and epinephrine on transcapillary fluid movement in normovolemic animals has been studied by several investigators (64,65,92). In skin and skeletal muscle of denervated cat hindlimbs, short-term, intravenous infusions of norepinephrine produced greater resistance increases in precapillary than postcapillary vessels causing a reduction in capillary hydrostatic pressure and a net fluid movement from the tissues into the microcirculation (92). In the dog forelimb, a net transcapillary fluid reabsorption occurs during short- and long-term intra-arterial infusion of norepinephrine (64,65). Epinephrine, when infused intra-arterially into the denervated cat hindlimb also constricted precapillary more than postcapillary vessels, causing a net reabsorption of extravascular fluid (92). Intra-arterial infusions of epinephrine in dog forelimbs produced increases in total and segmental resistances in skin and skeletal muscle along with decreases in forelimb weight which were sustained for 180 minutes of infusion (64,65).

Catecholamines, in addition to altering the pre- to postcapillary resistance ratio, can alter the rate of transcapillary fluid movement via their effects on functional capillary surface area (51,92,95). Topical applications of

both norepinephrine and epinephrine constricted precapillary sphincter vessels and presumably decreased the total surface area available for exchange (9). However, prolonged intravenous infusion of norepinephrine has been reported to increase functional capillary surface area as reflected by CFC measurements (92). The increased CFC was attributed to precapillary sphincter relaxation subsequent to the accumulation of vasodilator metabolites.

Although catecholamines can cause substantial changes in intra- and extravascular fluid distribution in skin and skeletal muscle, some investigators conclude that the influence of catecholamines on transcapillary fluid reabsorption during hemorrhage is minimal, since in cat skeletal muscle, fluid reabsorption during hemorrhage was not affected by adrenalectomy (96), or by isolating the preparation from the hemorrhaged cat except for neural connections (89). In addition, fluid reabsorption was not maintained during hemorrhage when the cat hindlimb was acutely denervated (96).

Angiotensin's role in regulating transcapillary fluid movement during hemorrhage has not been investigated thoroughly. Intra-arterial angiotensin infusion constricted precapillary more than postcapillary vessels in dog forelimbs (2,3,70) and hindpaws (2,3), and in cat hindlimbs (51). However, angiotensin caused a much smaller reabsorption of extravascular fluid than norepinephrine when administered in

equipressor doses (51). Mellander and Johanssen (95) have suggested that the relatively weak effects of angiotensin on transcapillary fluid reabsorption may be related to its strong constriction of precapillary sphincters which decreases capillary surface area available for exchange.

Vasopressin, like angiotensin, is reported to constrict precapillary more than postcapillary vessels in dog forelimbs (70,71) and hindlimbs (1,2), thereby reducing capillary hydrostatic pressure. However, vasopressin has been reported to produce much less fluid reabsorption than equipressor doses of norepinephrine (95). One explanation for the minimal effects of both vasopressin and angiotensin on transcapillary fluid reabsorption, is that both agents may have produced a marked constriction of small venules but not large veins. In dog forelimb studies (70,71), evidence that vasopressin and angiotensin increased the pre- to postcapillary resistance ratio were based primarily on measurements of large artery and large vein resistances. Resistances in the small vessel segment could not be separated into pre- and postcapillary components. Consequently, if the small venular resistance increased proportionately to arteriolar resistance, the pre- to postcapillary resistance ratio would remain relatively constant and little fluid reabsorption would occur. This hypothesis is supported by studies of the mesenteric microcirculation, which indicate that vasopressin caused strong contraction of venules (10).

Even though several studies of the effects of angiotensin and vasopressin on transcapillary fluid movement in skin and muscle have been conducted on normovolemic animals, the effects of these agents in hypovolemic animals have not been thoroughly evaluated.

D. Passive Responses; Indirect Effects of Neuro-humoral Control

In addition to neuro-humoral mechanisms which influence primarily the pre- and postcapillary resistance vessels and precapillary sphincters to alter capillary pressure and functional surface area, there are other factors that may be important in altering transcapillary fluid movement during hemorrhage. It is obvious from equation 3 that changes in tissue hydrostatic and osmotic pressures, and changes in plasma colloid osmotic pressure will also influence the direction and rate of fluid movement across capillaries. In addition, changes in arterial and venous pressures as a result of blood loss will influence capillary hydrostatic pressure and hence transcapillary fluid movement.

Hemorrhage which is severe enough to lower arterial and venous pressures tends to lower capillary hydrostatic pressure and produce extravascular fluid reabsorption, even if there is no change in the pre- to postcapillary resistance ratio or functional capillary surface area. The direct effect of reductions in arterial pressure on transcapillary fluid movement has been studied in normovolemic animals by

partially occluding the arterial supply to skeletal muscle vascular beds (54,98). Experiments by Öberg (98) and Folkow and Öberg (54) suggested that arterial pressure had to be reduced to at least 50-60 mm Hg in order to cause an appreciable fall in capillary hydrostatic pressure. The relative constancy of capillary pressure despite variations in arterial pressure was attributed to autoregulation of precapillary vessels due to the combined effects of vasodilator metabolite accumulation and reduced transmural pressure which tended to depress the inherent myogenic activity of precapillary resistance vessels causing them to relax. Relaxation of precapillary vessels would tend to decrease the pre- to postcapillary resistance ratio and cancel the expected changes in capillary pressure due to a fall in arterial pressure. Öberg (98) concluded that because of local vasodilator mechanisms, reductions in arterial pressure did not cause large decreases in capillary pressure until the precapillary vessels were maximally dilated. However, during hemorrhage, local dilator mechanisms are interfered with by neurally and humorally mediated vasoconstriction. Although reductions in arterial pressure may not alter capillary pressure greatly in the normovolemic animal, they may contribute significantly to the fall in capillary pressure in the hypovolemic animal. A fall in venous pressure during hemorrhage will also tend to reduce capillary pressure.

Changes in tissue hydrostatic and osmotic pressure and plasma osmotic pressure may also influence the direction and rate of transcapillary fluid movement during hemorrhage. Loss of fluid from the tissues to the circulation would tend to reduce tissue hydrostatic and plasma osmotic pressures, while increasing tissue osmotic pressure. All of these changes, however, would tend to oppose rather than aid in fluid reabsorption observed during hemorrhage. Recently, plasma hyperosmolarity due primarily to hyperglycemia, has been suggested to be an important factor in causing extravascular fluid reabsorption in skeletal muscle during prolonged hemorrhage (80,81). However, during mild or moderate hemorrhage, the most important factors governing the transcapillary movement of fluid appear to be changes in capillary pressure and capillary surface area (31,57,89,98).

METHODS

Adult mongrel dogs of either sex, weighing 16-20 kg, were anesthetized with sodium pentobarbital (30 mg/kg iv) and allowed to breathe unassisted through a cuffed endotracheal tube. Supplements of sodium pentobarbital were given as necessary during the surgical and experimental procedures.

Skin of the right forelimb was circumferentially sectioned approximately 5 cm above the elbow. The brachial artery and brachial and cephalic veins were isolated and the muscles and connective tissue sectioned with an electrocautery. The forelimb nerves (median, ulnar, radial, and musculocutaneous) were isolated and coated with an inert silicon spray (Antifoam A, Dow Corning, Midland, Michigan) to prevent drying. The humerus was cut and the ends of the marrow cavities packed with bone wax (Ethicon Inc., Somerville, New Jersey). Inflow to the forelimb was confined to the brachial artery and outflow to the brachial and cephalic veins.

After surgery was completed, sodium heparin (Wolins Pharmical Corp., Melville, New York) was administered in an initial dose of 700 USP units/kg body weight with hourly supplements of 300 USP units/kg body weight. Forelimb

intravascular pressures were measured from polyethylene (P.E.) cannulae (Intramedic tubing, Clay Adams) inserted into the following sites (as shown in Figure 1): 1) brachial artery via a side branch (P.E. 50; outside diameter (o.d.) = 0.038"); 2) skin small artery from the third superficial volar metacarpal artery (P.E. 60; o.d. = 0.048"); 3) muscle small artery from a vessel supplying a flexor muscle in the mid-portion of the forelimb (P.E. 50); 4) skin small vein from the second superficial dorsal metacarpal vein (P.E. 60); 5) muscle small vein from one of the deep vessels draining a flexor muscle in the mid-portion of the forelimb (P.E. 10; o.d. = 0.024"); 6) skin large vein from the cephalic vein via a side branch (P.E. 60); 7) muscle large vein from the brachial vein via a side branch (P.E. 60). The small artery catheters were inserted in a downstream direction, whereas the small vein catheters were inserted upstream. Since a cannulated small vessel acts as an extension of the catheter, the pressure measured from the catheter will be the same as that in the vessel to which the cannulated vessel connects. The measured pressure is accurate as long as the cannulated vessel is patent and unobstructed by valves, a condition which was verified in all experiments by withdrawing blood from and flushing saline into the cannulated vessel. The presence of the catheter is presumed not to alter measurably the pressure in the arterial or venous system, since, in the canine forelimb, the cannulated vessel is a negligible

Figure 1. Schematic of the canine forelimb preparation. Although the limbs were not skinned, the skin has been omitted from the upper portion of the diagram to better show the sites of pressure and flow measurements in this preparation.

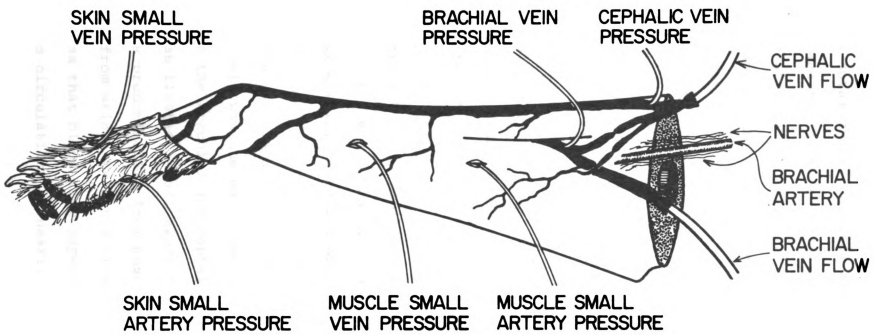
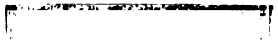

SKIN SMALL
VEIN PRESSURE
BRACHIAL VEIN
PRESSURE
CEPHALIC VEIN
PRESSURE
CEPHALIC
VEIN FLOW
NERVES
BRACHIAL
ARTERY
BRACHIAL
VEIN FLOW
SKIN SMALL
ARTERY PRESSURE
MUSCLE SMALL
VEIN PRESSURE
MUSCLE SMALL
ARTERY PRESSURE

Figure 1

fraction of the total cross sectional area of the arterial or venous bed, and there are abundant artery to artery and vein to vein anastomoses (70,71,97).

All cannulae used for pressure measurements were filled with saline and connected to Statham low volume displacement transducers (Model No. P23Gb, Statham Laboratories, Hato Rey, Puerto Rico) which were coupled to a Hewlett Packard direct writing oscillograph (Model No. 7784A, Hewlett Packard Co., Waltham, Massachusetts). The brachial and cephalic veins were partially transected and cannulated with 6-8" sections of P.E. 320 tubing (o.d. = 0.138"), downstream from the sites of large vein pressure measurements. Flow from both veins was directed into an open reservoir maintained at constant volume by a variable speed, roller pump (Lange Model RE 161, Extracorporeal Medical Specialties Inc., Mt. Laurel Township, New Jersey) which returned blood to the animal via a large vein. Forelimb blood flow was determined by timed collection of brachial and cephalic venous outflows. When the forelimb was prepared as described above, the median cubital vein was the major remaining anastomotic channel between the brachial and cephalic veins. The median cubital vein was ligated in all experiments so that brachial venous flow was predominantly from muscle and cephalic flow predominantly from skin. Evidence from several sources (35, 37,97) indicates that blood flow separation in the parallel skin and muscle circulations is nearly complete with this



preparation. According to Miller (98), the cephalic vein drains skin of the forepaw and antebrachium whereas muscles of the antebrachium are drained by branches of the median vein which becomes the brachial vein near the elbow. Daugherty et al. (37) report that serotonin, which is a potent constrictor in the cutaneous vasculature, but exerts little effect on skeletal muscle blood vessels (35), produces large reductions in cephalic vein flow and no consistent changes in brachial vein flow when infused into the brachial artery of the dog forelimb. Finally, the locally mediated vasodilator response which follows release of an arterial occlusion (reactive hyperemia), is well developed in skeletal muscle but poorly developed or absent in skin (27). In the dog forelimb, reactive hyperemia is pronounced in the vasculature drained by the brachial vein and minimal in vessels drained by the cephalic vein as illustrated in Figure 2.

In all experiments, total, arterial, small vessel, and venous resistances in muscle were calculated by dividing the appropriate pressure gradient by brachial vein flow. Total and segmental vascular resistances in skin were calculated by dividing cutaneous pressure gradients by cephalic vein flow. A more complete description of vascular resistance calculations for the forelimb is contained in Appendix B.

Mean intraluminal pressure in each vascular segment of skin and skeletal muscle was calculated as:

Figure 2. Peak brachial (cross-hatched bars) and cephalic venous (white bars) flow rates (expressed as percent of control) in 3 dogs after the release of 1 and 3 minute brachial artery occlusions (indicated by the numbers 1 and 3 above the bars).

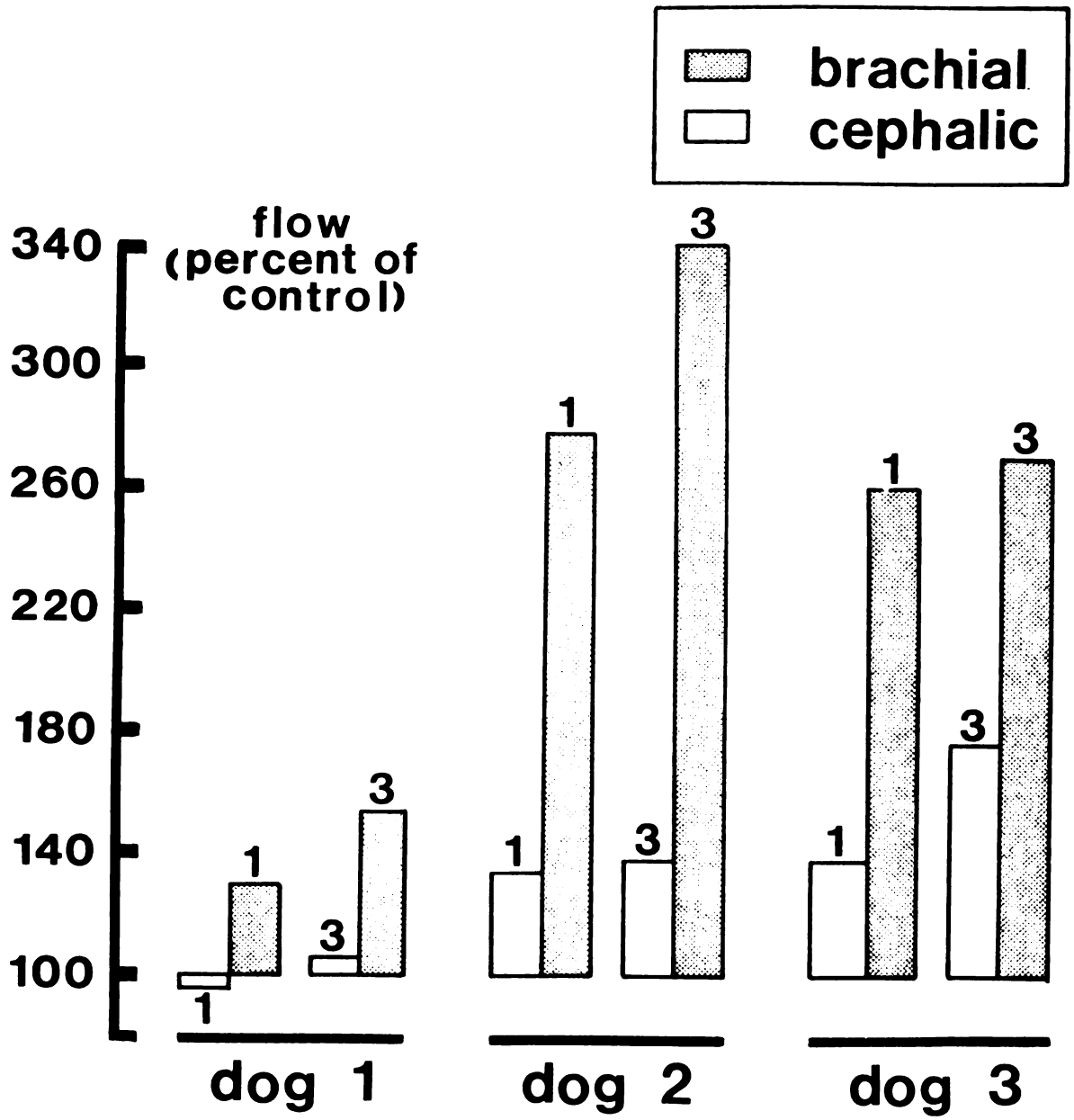

brachial
cephalic
flow
(percent of
control)
340
300
260
220
180
140
100
1
3
1
3
1
3
1
3
1
3
dog 1
dog 2
dog 3

Figure 2

$$\bar{P} = \frac{P_1 + P_2}{2}$$

where: $\bar{P}$ = mean intraluminal pressure

P_1 = inflow pressure

P_2 = outflow pressure.

Since transmural pressure equals intraluminal pressure minus tissue hydrostatic pressure, mean intraluminal pressure can be used to approximate mean transmural pressure if the tissue pressure is assumed to remain nearly constant at about 0 mm Hg.

In some experiments, changes in forelimb weight were recorded by placing the limb on a plastic grid platform attached to a calibrated strain gauge balance which was coupled to a direct writing oscillograph. A 2 g weight usually produced a 10-15 mm pen deflection on the oscillograph. Observations of forelimb weight and vascular resistances were used to estimate changes in intravascular volume and net transcapillary fluid movement. A rapid weight loss associated with large increases in vascular resistance was attributed largely to decreased intravascular volume. However, slower, prolonged weight loss associated with steady or decreasing vascular resistance was attributed to net transcapillary fluid reabsorption.

Mean systemic arterial pressure was measured in all experiments from a P.E. 240 catheter inserted into the lower abdominal aorta via the right femoral artery. In some experiments, arterial systolic and diastolic pressures were recorded

and pulse pressure calculated as the difference between systolic and diastolic pressures. Central venous pressure was measured in some experiments from a P.E. 320 catheter inserted into the left jugular vein and advanced to within 2-3 cm of the right atrium.

Series I: Naturally perfused, innervated forelimbs; local hypotension and rapid arterial hemorrhage

In 16 dogs, the forelimb nerves were left intact. After a 30 minute control period, mean forelimb perfusion pressure was reduced to 100 mm Hg by compression of the brachial artery with a screw clamp. Changes in limb weight were recorded continuously and pressure-flow determinations were obtained 1, 3, and 5 minutes after mean brachial artery pressure had stabilized at 100 mm Hg. This procedure for pressure, flow, and weight measurements was repeated after forelimb perfusion pressure had been reduced to 75, 50, and 35 mm Hg by further tightening of the screw clamp. In some experiments, pressure-flow determinations were made every 2 minutes for a total of 20 minutes at each of these forelimb perfusion pressures (100, 75, 50, and 35 mm Hg). The clamp was then released so that brachial artery pressure and venous outflows returned to their pre-clamp control levels. After a recovery period, which was terminated when pressures, flows, and forelimb weight had stabilized, brachial artery pressure was reduced in steps to 100, 75, 50, and 35

mm Hg by rapid bleeding from a carotid artery into a pressurized reservoir. The protocol for measuring changes in forelimb weight, intravascular pressures, and venous outflows was identical to that described for the preceding clamp period.

Series II: Naturally perfused, denervated forelimbs; local hypotension and rapid arterial hemorrhage

In 17 dogs, the forelimb nerves were coated with a local anesthetic (Cetacaine, Cetylite Industries., Long Island City, New York) and severed 3-5 cm above the elbow. Pressure-flow determinations were made immediately before and at 5, 10, 15, and 20 minutes after denervation. Twenty-five minutes after the nerves had been cut, forelimb perfusion pressure was reduced in steps to 100, 75, 50, and 35 mm Hg by clamping the brachial artery. Pressure-flow determinations were obtained 1, 3, and 5 minutes after mean brachial artery pressure had stabilized at each of these pressures (100, 75, 50, and 35 mm Hg). The clamp was released, and after a recovery period, brachial artery pressure was reduced in steps to 100, 75, 50, and 35 mm Hg by rapid bleeding from a carotid artery into a pressurized reservoir, and intravascular pressures and venous outflows determined according to the protocol described for Series I.

Series III: Cross-perfused forelimbs; rapid arterial hemorrhage of recipient and donor dogs

The right forelimbs of 5 recipient dogs (16-20 kg) were prepared as described above, leaving the nerves intact, and perfused with blood from the carotid arteries of 5 donor dogs (25-30 kg) by using a variable speed roller pump (Lange Model RE 161, Extracorporeal Medical Specialties Inc., Mt. Laurel Township, New Jersey). Blood samples from the donor and recipient dogs were cross-matched and cross-typed to minimize transfusion reactions.

During the control period, forelimb perfusion pressure was set at 100-125 mm Hg with a servosystem (Figure 3) which continuously adjusted the flow rate of the perfusion pump to maintain brachial artery pressure constant. After a 20-30 minute control period, the recipient dog was rapidly bled from a carotid artery into a pressurized reservoir so that its mean systemic arterial pressure was reduced in steps to 100, 75, 50, and 35 mm Hg. At each step reduction in systemic arterial pressure, the set-point of the servo-system was altered so that brachial artery pressure matched the recipient dog's systemic arterial pressure, and forelimb intravascular pressures and venous outflows were then determined every 3 minutes for 15 minutes. As long as the donor dog remained normotensive and normovolemic, this cross-circulation technique eliminated the hemorrhaged-induced accumulation of circulating vasoconstrictors in the arterial

Figure 3. Schematic of the servosystem used to control brachial artery pressure.

1. Set point circuit--establishes a reference voltage which is compared to the voltage from the AC amplifier. When the controlled variable deviates from set point, an error voltage is developed.

2. Control panel adjustments--adds adjustable proportional gain, reset and rate, or lag functions to the error and feedback voltages. The feedback voltage is derived from the output current of the controller.

3. Control amplifier--compares the modified error and feedback voltages and provides an output voltage proportional to the difference voltage.

4. C.A.T. (Current Adjusting Type) output Control--provides and maintains a current output at a constant operating level in the absence of a voltage from the amplifier; varies the output current according to polarity and amplitude of the amplifier output signal.

5. Automatic-Manual (A-M) switching circuits--transfers the control system bumplessly between automatic and manual modes, and permits manual adjustment of the final control element position in the manual mode. With automatic mode, perfusion pump speed is controlled to maintain perfusion pressure constant; with manual mode, constant flow perfusion is maintained.

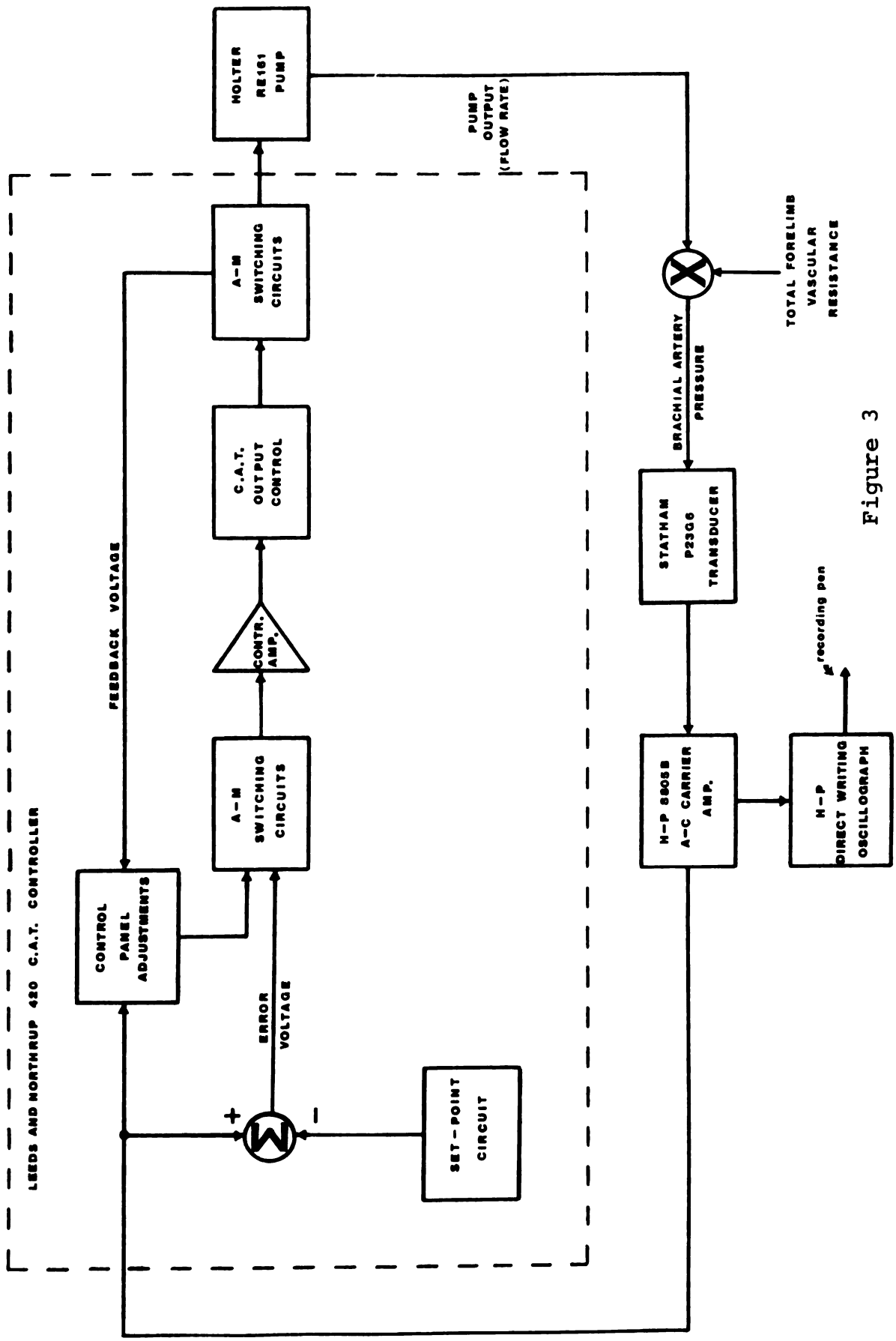

HOLTER RE161 PUMP
PUMP OUTPUT (FLOW RATE)
A-M SWITCHING CIRCUITS
C.A.T. OUTPUT CONTROL
CONTR. AMP.
FEEDBACK VOLTAGE
A-M SWITCHING CIRCUITS
CONTROL PANEL ADJUSTMENTS
ERROR VOLTAGE
SET-POINT CIRCUIT
LEEDS AND NORTHRUP 420 C.A.T. CONTROLLER
TOTAL FORELIMB VASCULAR RESISTANCE
BRACHIAL ARTERY PRESSURE
STATHAM P23G6 TRANSDUCER
H-P 8805B A-C CARRIER AMP.
recording pen
H-P DIRECT WRITING OSCILLOGRAPH

Figure 3

supply of the recipient forelimb, and permitted examination of the ability of sympathetic nerves alone to elicit vasoconstriction in the forelimb.

The shed blood was reinfused into the recipient dog, the forelimb nerves were severed, and forelimb intravascular pressures and venous outflows allowed to stabilize. The donor dog was then rapidly bled so that its mean systemic arterial pressure was reduced to 100, 75, 50, and 35 mm Hg in steps, and brachial artery pressure in the forelimb of the recipient dog was reduced to corresponding levels by adjusting the set-point of the servosystem. Forelimb intravascular pressures and venous outflows were determined according to the protocol described for bleeding of the recipient dog. Since the recipient dog was maintained normotensive and normovolemic, and since the forelimb nerves were severed, changes in forelimb vascular resistance were due only to the passive effects of reducing forelimb perfusion pressure, and to the effects of circulating vasoconstrictors released from the hemorrhaged donor dogs.

Series IV: Naturally perfused, innervated or denervated forelimbs; slow, continuous hemorrhage

The right forelimbs of 17 dogs (8 innervated and 9 denervated) were prepared as described above. After a control period, the animals were hemorrhaged by continuous withdrawal of 0.41 ml blood/kg body weight per minute from

the femoral vein using a variable speed roller pump. Central venous pressure was measured continuously and forelimb venous outflows and intravascular pressures as well as arterial mean and pulse pressures, were measured at 2 minutes intervals for 60 minutes during the hemorrhage period.

DATA ANALYSIS

Control means (vascular resistances, rate of forelimb weight change, and intravascular pressures) were compared with experimental means (produced by local hypotension or hemorrhage) using a Dunnett's t test modified for unequal variances. To analyze whether hemorrhage and local hypotension produced significantly different values of a given parameter, a Student's t test for paired observations was used. Differences between innervated and denervated forelimb vascular resistance and weight responses to hemorrhage were analyzed using Welch's t' test for unpaired observations and unequal variances. In Series III, differences in forelimb vascular resistances elicited by bleeding the donor and recipient dogs were analyzed with a Mann-Whitney U test. For all comparisons, differences between means were considered significant only if the probability of making a type I error (α) was less than 0.05. A more detailed description of the statistical methods used is presented in Appendix C.

RESULTS

I. Series I: Naturally Perfused, Innervated Forelimbs; Effects of Local Hypotension and Rapid Arterial Hemorrhage

A. Forelimb Weight

Changes in forelimb weight observed in a selected experiment when perfusion pressure was lowered by clamping the brachial artery and by arterial hemorrhage are shown in Figure 4. When forelimb perfusion pressure was reduced from 116 mm Hg to 100 mm Hg by clamping the brachial artery, there was an initial rapid weight loss followed by a slower, sustained loss. This response pattern was repeated when brachial artery pressure was subsequently lowered from 100 to 75, from 75 to 50, and from 50 to 35 mm Hg. When brachial artery pressure was reduced from 116 to 100 mm Hg by hemorrhage, there was again a rapid phase of weight loss, followed by a slower sustained loss. This pattern was also repeated during subsequent brachial artery pressure reductions by hemorrhage. At each pressure reduction, both the rapid and slow phases of weight loss are greater during hemorrhage than during the corresponding clamp periods.

Data reported in Figure 5 are mean values and standard errors (S.E.) from 16 experiments for the slow sustained

Figure 4. Changes in forelimb weight (grams; ordinate) during local hypotension (solid dots) and rapid arterial hemorrhage (circles). C = control period (10 minutes). Circled numbers (100, 75, 50, and 35) refer to steady state brachial artery pressures (mm Hg) at which weight changes were determined. Data is from a selected experiment using an innervated forelimb.

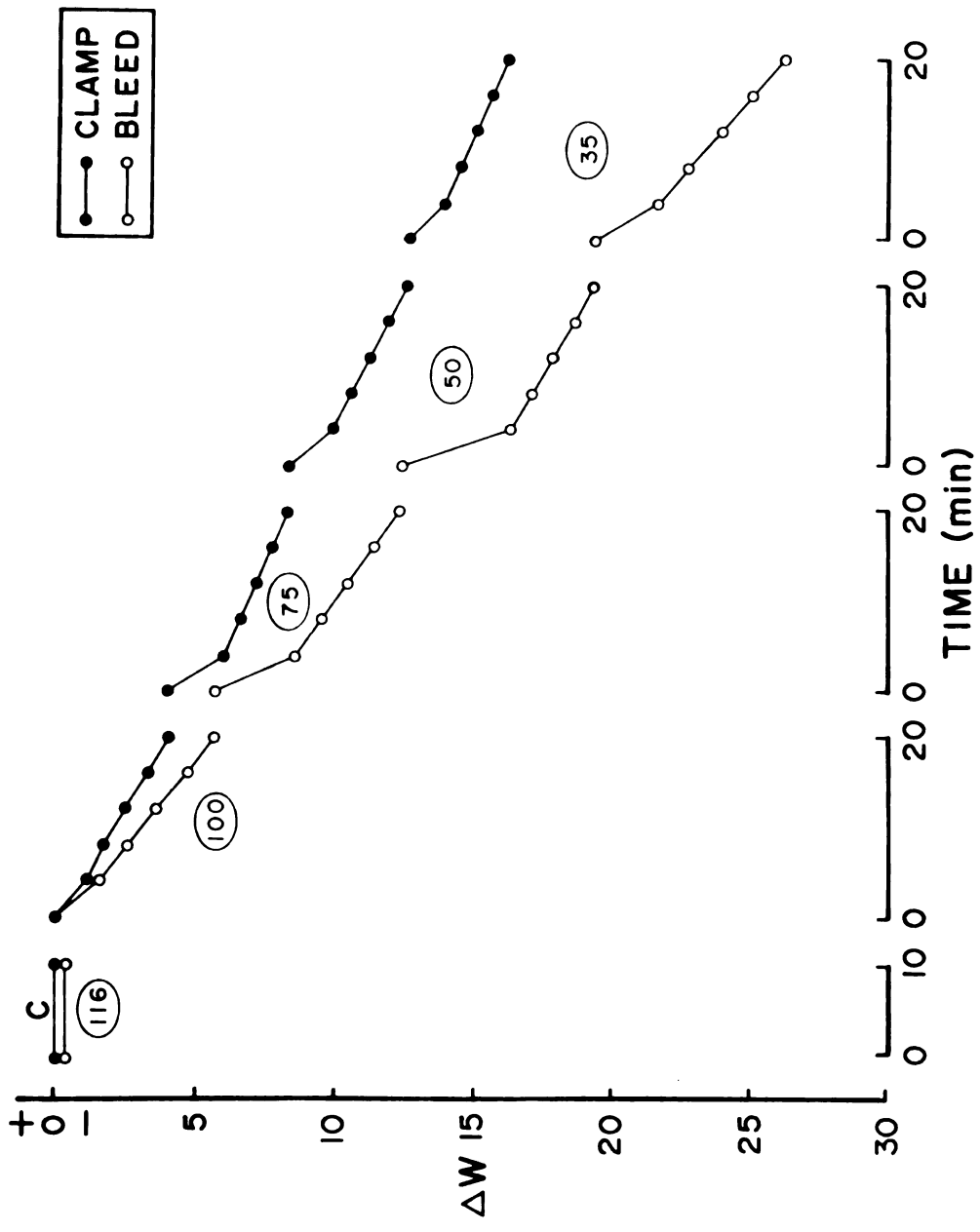

CLAMP
BLEED
C
116
100
75
50
35
+
0
−
5
10
15
20
25
30
ΔW
0
10 0
20 0
20 0
20 0
20
TIME (min)

Figure 4

Figure 5. Slow, sustained changes in weight (ordinate; grams per minute) of innervated forelimbs during local hypotension (white bars) or rapid arterial hemorrhage (cross-hatched bars). Data represent means ± standard errors from 16 experiments. Abscissa represents brachial artery pressure (P_{BA}) in mm Hg. Forelimb weight = 529.1 ± 29.6 g.

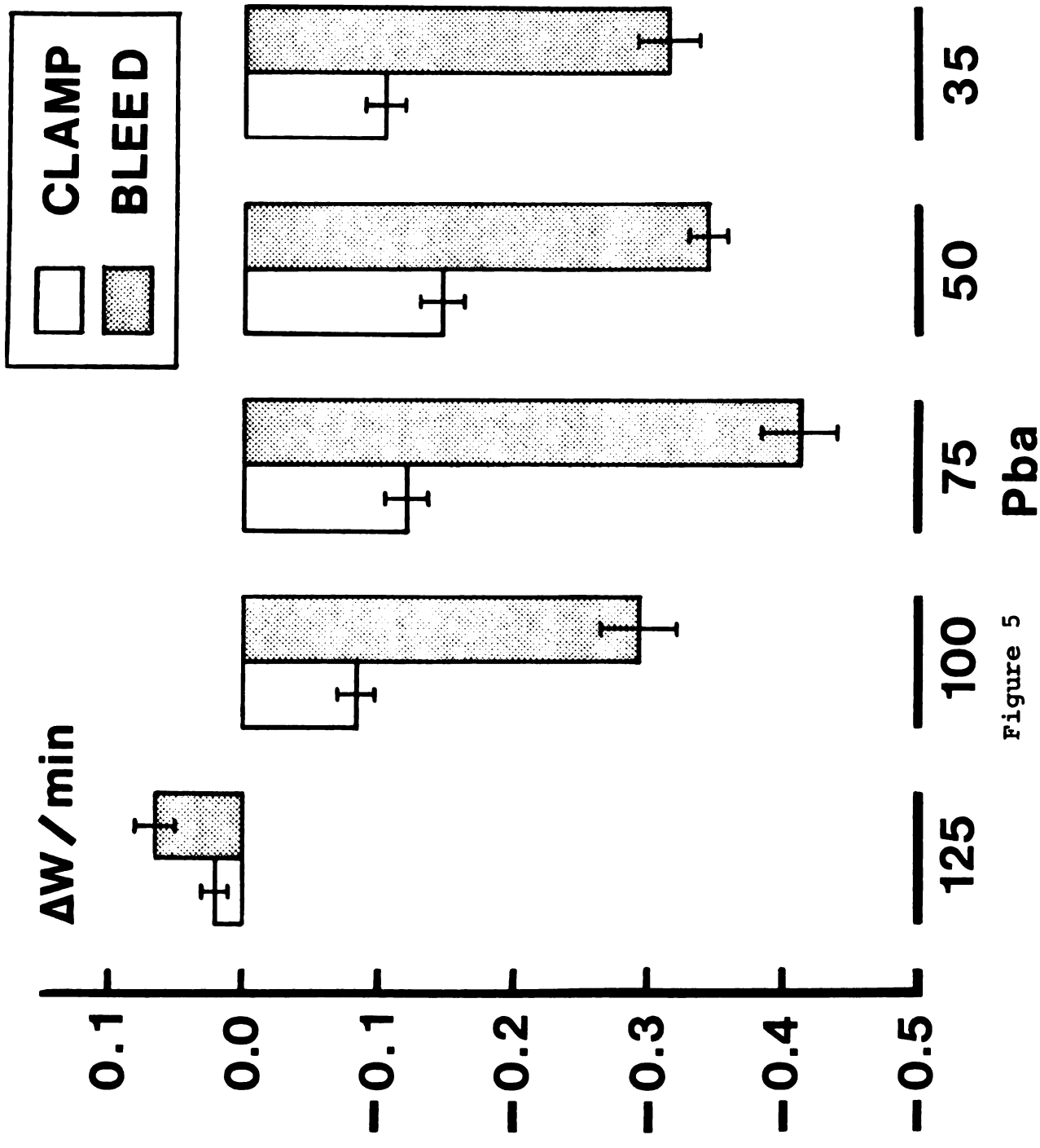


Figure 5

phases of weight losses. Since these weight losses continued after vascular resistances and arterial and venous pressures had stabilized, they were attributed to extravascular fluid reabsorption, rather than to a reduction in intravascular blood volume. There was a significant, sustained weight loss at all levels of hypotension produced either by clamping the brachial artery or by arterial hemorrhage. However, the weight losses during hemorrhage were always significantly greater than those observed at corresponding pressures during clamping. Local hypotension induced by clamping the brachial artery produced a maximum rate of weight loss of 0.15 $\pm$ 0.02 g/min at a forelimb perfusion pressure of 50 mm Hg, whereas at this same pressure, hemorrhagic hypotension produced a 0.34 $\pm$ 0.03 g/min weight loss.

B. Intraluminal Pressures

Data in Tables 1 and 2 are mean intraluminal pressures in all forelimb vascular segments when forelimb perfusion pressure was reduced by clamping the brachial artery or by arterial hemorrhage. Mean intraluminal pressure decreased significantly in all forelimb vascular segments during clamping and during bleeding. Except in the large skin veins, the reductions in intraluminal pressure in skin and muscle vascular segments produced by hemorrhage were not significantly different than those produced by clamping the brachial

Table 1. Effects of local hypotension and rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) in innervated skin arteries (SA), small vessels (SSV), and veins (SV). P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 16 experiments.

	P_{BA}	$\bar{P}_{SA}$	$\bar{P}_{SSV}$	$\bar{P}_{SV}$
Control	122.3±2.8	110.9±2.8	56.0±1.6	9.9±0.5
Clamp	100.0±0.5	91.3±0.8	46.6±0.8	7.9±0.7
	76.1±0.6	69.2±0.6	35.0±0.6	5.5±0.4
	51.9±0.5	46.9±0.5	23.9±0.5	3.7±0.4
	34.8±0.6	31.2±0.6	16.0±0.4	2.7±0.4
Control	123.3±2.9	110.5±3.0	55.7±1.7	10.5±0.6
Bleed	98.9±0.6	91.1±0.7	45.6±0.6	5.4±0.4
	74.2±0.6	67.3±0.8	33.1±0.7	3.6±0.3
	50.5±0.7	45.6±0.7	22.6±0.5	2.2±0.4
	35.9±0.5	32.4±0.6	16.6±0.4	2.0±0.4

Table 2. Effects of local hypotension and rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) in innervated muscle arteries (MA), small vessels (MSV), and veins(MV). P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 16 experiments.

	P_{BA}	$\bar{P}_{SA}$	$\bar{P}_{SSV}$	$\bar{P}_{SV}$
Control	122.3±2.8	112.9±2.8	53.2±1.6	5.8±0.3
Clamp	100.0±0.5	93.2±0.7	45.8±0.8	4.0±0.3
	76.1±0.6	70.3±0.7	35.0±0.4	3.2±0.3
	51.9±0.5	47.5±0.6	23.3±0.5	2.4±0.3
	34.8±0.6	31.4±0.5	15.5±0.4	1.9±0.3
Control	123.3±2.9	114.4±2.9	55.5±1.7	6.2±0.4
Bleed	98.9±0.6	93.8±0.7	46.4±0.5	3.2±0.3
	74.2±0.6	69.8±0.5	34.7±0.4	2.8±0.3
	50.5±0.7	46.4±0.6	22.5±0.4	2.5±0.3
	35.9±0.5	32.2±0.6	15.9±0.5	2.2±0.3

artery to corresponding pressures. In the large skin veins, hemorrhage produced slightly greater reductions in intraluminal pressure at brachial artery pressures of 100 and 75 mm Hg, but not at 50 and 35 mm Hg.

C. Skin Total and Segmental Vascular Resistances

Data in Figure 6 report total and segmental resistances in the skin vasculature as functions of brachial artery pressure when forelimb perfusion pressure was reduced by clamping the brachial artery or by hemorrhage. When forelimb perfusion pressure was reduced by clamping the brachial artery, resistance in all cutaneous vascular segments did not change significantly until brachial artery pressure fell to 50 and 35 mm Hg. Skin venous resistance increased from a control value of 0.09 $\pm$ 0.01 to 0.19 $\pm$ 0.02 and 0.30 $\pm$ 0.04 at brachial artery pressures 50 and 35 mm Hg respectively. Clamping the brachial artery did not produce any significant changes in skin arterial and small vessel resistances.

When forelimb perfusion pressure was lowered by hemorrhage, total and segmental vascular resistances in skin increased significantly at all brachial artery pressures of 100 mm Hg and below. Total skin resistance increased progressively from a control value of 2.13 $\pm$ 0.16 to 19.04 $\pm$ 3.81 at a brachial artery pressure of 35 mm Hg. Most of this increase was due to constriction of the small vessel segment, where resistance increased from a control value of 1.61 $\pm$

Figure 6. Effects of local hypotension (solid dots) and rapid arterial hemorrhage (circles) on skin total, arterial, small vessel, and venous resistances in innervated forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-clamp and pre-hemorrhage control values. Data represent means $\pm$ standard errors from 16 experiments.

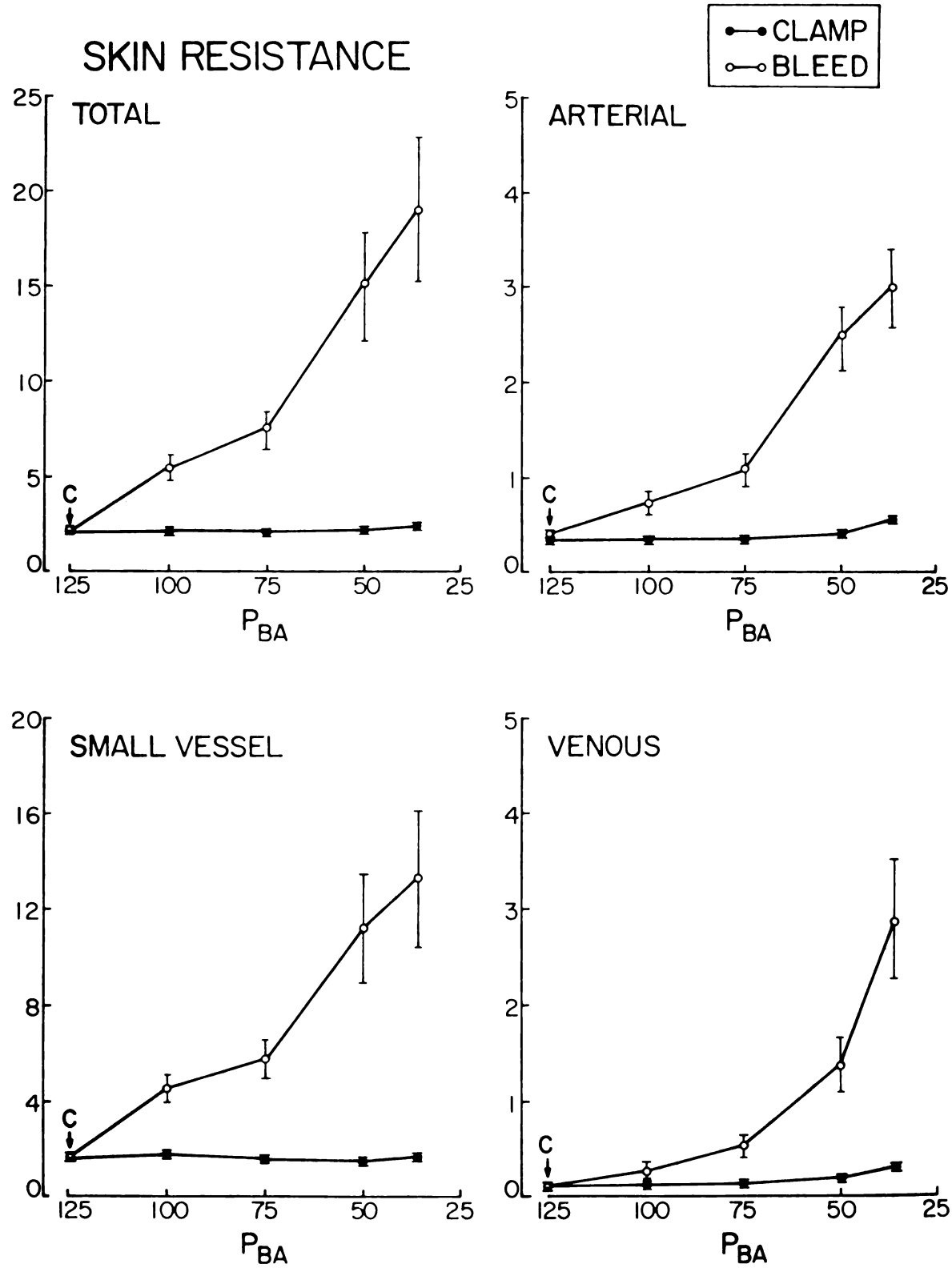

SKIN RESISTANCE
CLAMP
BLEED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
125
100
75
50
25
P_{BA}

Figure 6

0.14 to 13.23 ± 2.92 at a brachial artery pressure of 35 mm Hg. However, as shown in Table 3 the large veins constricted proportionately more than the small vessels during hemorrhage. At a brachial artery pressure of 35 mm Hg, skin venous resistance was more than 24 times greater than control. Total and all segmental resistances during hemorrhage were significantly greater than those observed at corresponding pressures during clamping.

D. Muscle Total and Segmental Vascular Resistances

Changes in total and segmental resistances in the muscle vasculature during local hypotension produced by clamping the brachial artery, and during hemorrhagic hypotension are illustrated in Figure 7. Local hypotension elicited significant increases in muscle total, small vessel, and venous resistances at brachial artery pressures of 75, 50, and 35 mm Hg. Arterial resistance in muscle increased significantly only at brachial artery pressures of 50 and 35 mm Hg. Muscle total, arterial, small vessel, and venous resistances increased from control values of 3.02 ± 0.24, 0.49 ± 0.05, 2.37 ± 0.24, 0.10 ± 0.02 to 6.49 ± 0.45, 1.35 ± 0.14, 4.19 ± 0.21, and 0.38 ± 0.03 respectively at a brachial artery pressure of 35 mm Hg.

When forelimb perfusion pressure was reduced by hemorrhage, total and all segmental vascular resistances in muscle increased progressively above control values as brachial

Table 3. Effects of local hypotension and rapid arterial hemorrhage on skin total (ST), arterial (SA), small vessel (SSV), and venous (SV) resistances (R) (expressed as percent of control) in innervated forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 16 experiments.

	P_{BA}	R_{ST} %	R_{SA} %	R_{SSV} %	R_{SV} %
Control	122.3	100	100	100	100
Clamp	100.0	104	95	105	114
	76.1	95	97	93	126
	51.9	100	114	92	195
	34.8	117	154	98	306
Control	123.3	100	100	100	100
Bleed	98.9	258	170	282	233
	74.2	345	263	358	455
	50.5	702	597	696	1160
	35.9	893	732	822	2475

Figure 7. Effects of local hypotension (solid dots) and rapid arterial hemorrhage (circles) on muscle total, arterial, small vessel, and venous resistances in innervated forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-clamp and pre-hemorrhage control values. Data represent means $\pm$ standard errors from 16 experiments.

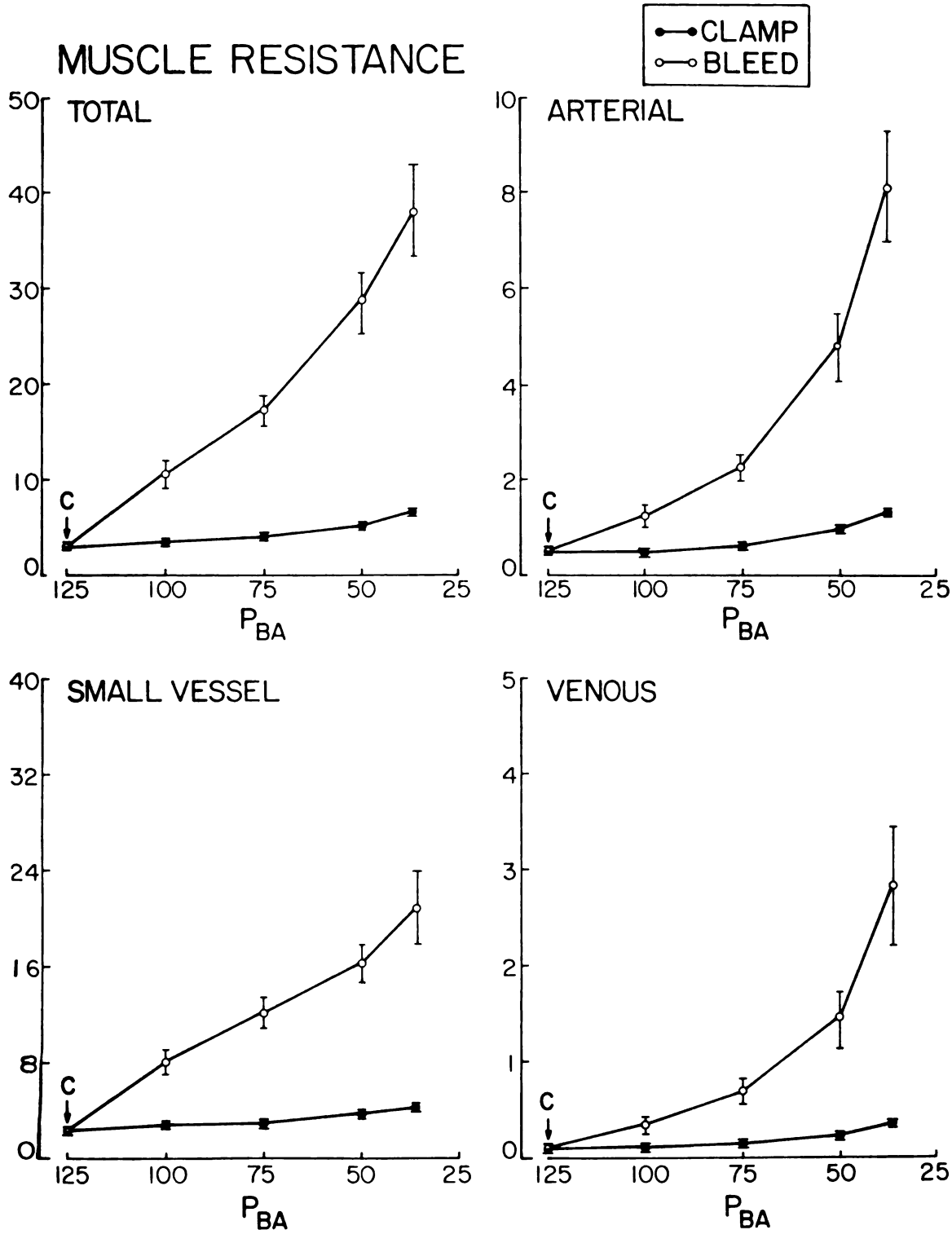

MUSCLE RESISTANCE
CLAMP
BLEED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
125
100
75
50
25
P_{BA}

Figure 7

Table 4. Effects of local hypotension and rapid arterial hemorrhage on muscle total (MT), arterial (MA), small vessel (MSV), and venous (MV) resistances (R) (expressed as percent of control) in innervated forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 16 experiments.

	P_{BA}	R_{MT} %	R_{MA} %	R_{MSV} %	R_{MV} %
Control	122.3	100	100	100	100
Clamp	100.0	122	105	121	124
	76.1	138	132	126	150
	51.9	176	191	156	223
	34.8	215	274	176	362
Control	123.3	100	100	100	100
Bleed	98.9	336	248	337	318
	74.2	539	444	506	650
	50.5	906	974	680	1377
	35.9	1207	1670	870	2703

artery pressure was reduced to 35 mm Hg. At a brachial artery pressure of 35 mm Hg, total muscle vascular resistance was increased more than 12 times above the control value. As in the skin, most of this increase in total muscle vascular resistance was due to constriction of the small vessel segment. However, the large artery and venous segments constricted proportionately more than the small vessel segment as illustrated in Table 4.

At each brachial artery pressure reduction during hemorrhage, total and all segmental vascular resistances in muscle were significantly greater than those observed at corresponding pressures during clamping.

II. Series II: Naturally Perfused, Denervated Forelimbs; Effects of Local Hypotension and Rapid Arterial Hemorrhage

A. Forelimb Weight

Mean values and standard errors from 17 experiments for the slow sustained weight losses observed during local hypotension and during rapid arterial hemorrhage are reported in Figure 8. During the clamp and hemorrhage control periods, the forelimbs were gaining weight at rates of 0.15 $\pm$ 0.03 and 0.14 $\pm$ 0.02 g/min respectively. There was a significant, sustained weight loss below control values at all levels of hypotension produced either by clamping the brachial artery or by arterial hemorrhage. The weight losses at brachial

Figure 8. Slow, sustained changes in weight (ordinate; grams per minute) of denervated forelimbs during local hypotension (white bars) or rapid arterial hemorrhage (cross-hatched bars). Data represents means ± standard errors from 17 experiments. Abscissa represents brachial artery pressure (P_{BA}) in mm Hg. Forelimb weight = 508.8 ± 18.9 g.

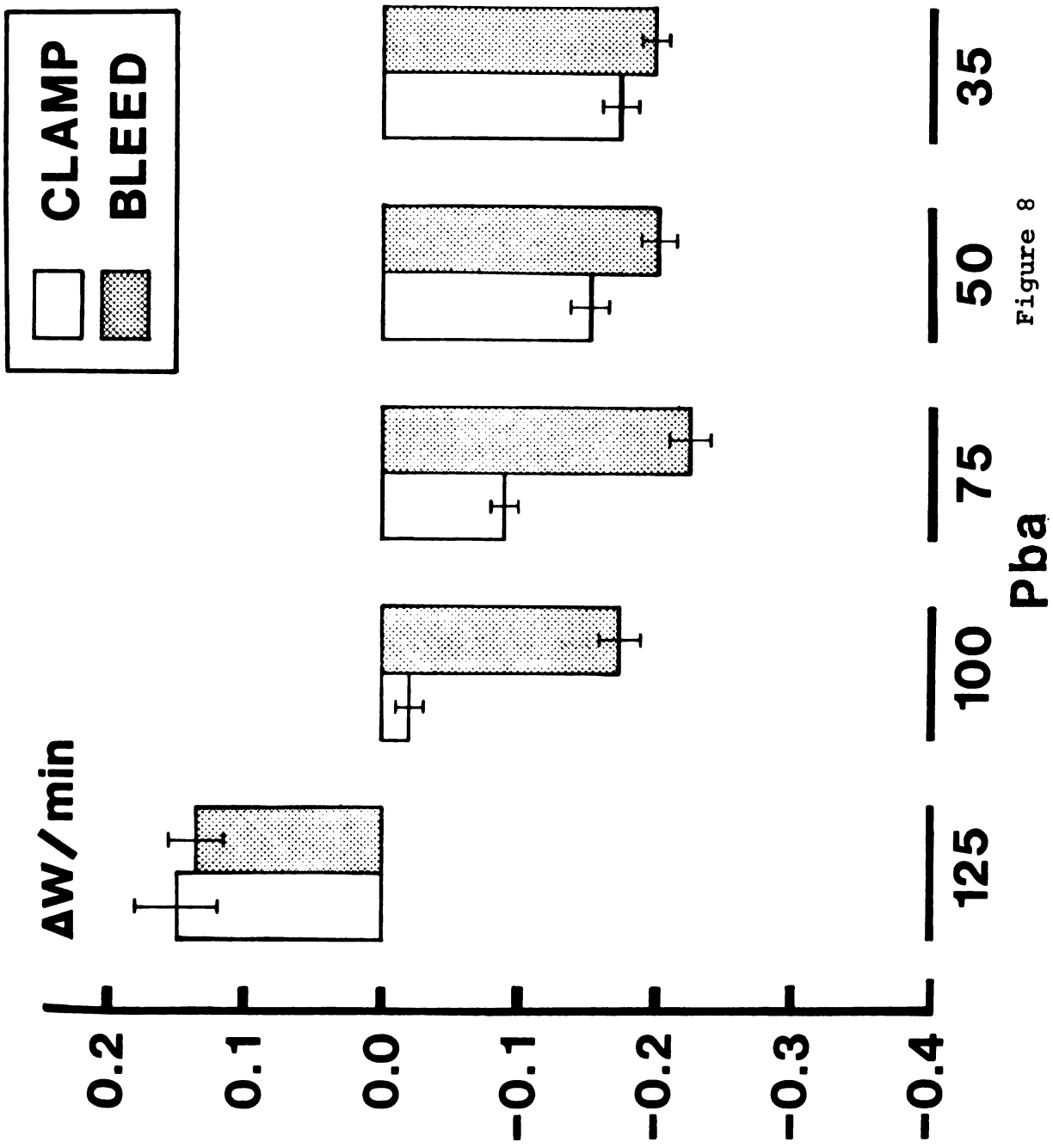


Figure 8

artery pressures of 100 and 75 mm Hg during hemorrhage were significantly greater than those observed at corresponding pressures during clamping. However, at brachial artery pressures of 50 and 35 mm Hg, the weight losses during clamping and bleeding were not statistically different. Comparisons of weight changes of innervated and denervated forelimbs during local hypotension and during rapid arterial hemorrhage are shown in Table 5. Since the denervated limbs were gaining weight during the control periods, the weight changes in both innervated and denervated forelimbs were normalized as experimental weight change minus weight change during the control period. During clamping, the rate of weight loss in denervated forelimbs was significantly greater than in innervated limbs at brachial artery pressures of 50 and 35 mm Hg. However, during hemorrhage, weight losses were not statistically different in innervated and denervated limbs.

B. Mean Intraluminal Pressures

Mean intraluminal pressures in all forelimb vascular segments before and after denervation, during local hypotension produced by clamping the brachial artery, and during systemic hypotension induced by arterial hemorrhage are reported in Tables 6 and 7. Denervation significantly reduced mean intraluminal pressure in skin and muscle arterial and small vessel segments, and increased mean intraluminal

Table 5. Effects of local hypotension and rapid arterial hemorrhage on slow, sustained changes in weight (grams per minute; Δ wt.) of innervated (N=16) or denervated (N=17) forelimbs. Weight changes were expressed as experimental weight change minus weight change during the control period. Values are means ± standard errors. P_{BA} = brachial artery pressure. Innervated Forelimb weight = 529.1 ± 29.6 g; Denervated Forelimb weight = 508.8 ± 18.9 g.

	Innervated		Denervated	
	P_{BA}	Δ wt.	P_{BA}	Δ wt.
Control	122.3±2.8	0.00	114.7±2.1	0.00
Clamp	100.0±0.5	-0.11±0.02	99.3±0.5	-0.19±0.04
	76.1±0.6	-0.15±0.03	76.4±0.4	-0.24±0.05
	51.9±0.5	-0.17±0.03	51.0±0.4	-0.30±0.05
	34.8±0.6	-0.13±0.03	34.4±0.4	-0.32±0.06
Control	123.3±2.9	0.00	116.6±1.9	0.00
Bleed	98.9±0.6	-0.34±0.05	100.0±0.9	-0.32±0.04
	74.2±0.6	-0.48±0.05	76.7±0.3	-0.36±0.05
	50.5±0.7	-0.41±0.03	52.9±0.3	-0.34±0.05
	35.9±0.5	-0.39±0.05	35.7±0.3	-0.33±0.05

Table 6. Effects of denervation, local hypotension, and rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) in skin arteries (SA), small vessels (SSV), and veins (SV). P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 17 experiments.

	P_{BA}	$\bar{P}_{SA}$	$\bar{P}_{SSV}$	$\bar{P}_{SV}$
		BEFORE DENERVATION		
Control	122.7±1.7	109.0±1.7	54.4±1.1	9.9±0.4
		AFTER DENERVATION		
Control	114.7±2.1	92.6±1.7	45.1±1.0	14.9±0.6
Clamp	99.3±0.5	80.2±1.3	38.0±1.1	11.1±0.5
	76.4±0.4	62.9±0.8	30.4±0.6	8.3±0.3
	51.0±0.4	41.8±0.4	19.9±0.4	4.8±0.3
	34.4±0.4	27.8±0.4	13.3±0.3	2.8±0.2
Control	116.6±1.9	92.8±1.7	45.4±1.0	16.8±0.9
Bleed	100.0±0.9	84.3±1.5	40.3±1.1	8.7±0.6
	76.7±0.3	67.7±0.8	33.4±0.7	4.9±0.4
	52.9±0.3	48.1±0.7	24.4±0.7	2.3±0.3
	35.7±0.3	33.4±0.4	17.8±0.4	1.3±0.3

Table 7. Effects of denervation, local hypotension, and rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) in muscle arteries (MA), small vessels (MSV), and veins (MV). P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 17 experiments.

	P_{BA}	$\bar{P}_{MA}$	$\bar{P}_{MSV}$	$\bar{P}_{MV}$
		BEFORE DENERVATION		
Control	122.7±1.7	114.2±1.8	56.7±1.0	6.9±0.4
		AFTER DENERVATION		
Control	114.7±2.1	104.8±2.1	52.5±1.2	8.8±0.4
Clamp	99.3±0.5	89.5±0.9	44.1±0.7	7.5±0.5
	76.4±0.4	69.7±0.6	34.8±0.5	5.3±0.3
	51.0±0.4	45.2±0.6	22.6±0.4	3.7±0.3
	34.4±0.4	29.6±0.5	14.7±0.4	2.8±0.3
Control	116.6±1.9	105.2±1.9	52.4±1.3	10.3±0.7
Bleed	100.0±0.9	91.2±1.2	44.9±1.0	5.9±0.6
	76.7±0.3	70.7±0.6	34.5±0.5	3.5±0.3
	52.9±0.3	48.3±0.6	24.3±0.4	2.9±0.3
	35.7±0.3	31.9±0.5	16.3±0.4	2.8±0.3

pressure in skin and muscle venous segments. Mean intraluminal pressure was significantly reduced below postdenervation control values in all forelimb vascular segments during clamping and during bleeding. Clamping the brachial artery to 75, 50, and 35 mm Hg produced greater reductions of mean intraluminal pressures in the skin arteries and small vessels than did bleeding to the same brachial artery pressures. At brachial artery pressures of 75, 50, and 35 mm Hg, hemorrhage produced greater reductions in skin venous intraluminal pressure than did clamping to corresponding brachial artery pressures. In skeletal muscle, at brachial artery pressures of 50 and 35 mm Hg, local hypotension produced greater reductions in arterial and small vessel intraluminal pressures than did hemorrhage. However, muscle venous mean intraluminal pressure was not significantly different during hemorrhage and local hypotension at any of the brachial artery pressures studied.

C. Skin Total and Segmental Vascular Resistances

Total and segmental resistances in the cutaneous vasculature of 17 forelimbs before and after denervation, and during hypotension produced either by clamping the brachial artery or by arterial hemorrhage are shown in Figure 9. When the forelimb nerves were sectioned (indicated by the first arrow on each graph), total skin resistance decreased from 1.41 $\pm$ 0.07 immediately before denervation to

Figure 9. Effects of denervation (first arrow on each graph), local hypotension (solid dots), and rapid arterial hemorrhage (circles) on skin total, arterial, small vessel, and venous resistances. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg and time in minutes (MIN) after denervation. C = pre-clamp and pre-hemorrhage control values. Data represent means $\pm$ standard errors from 17 experiments.

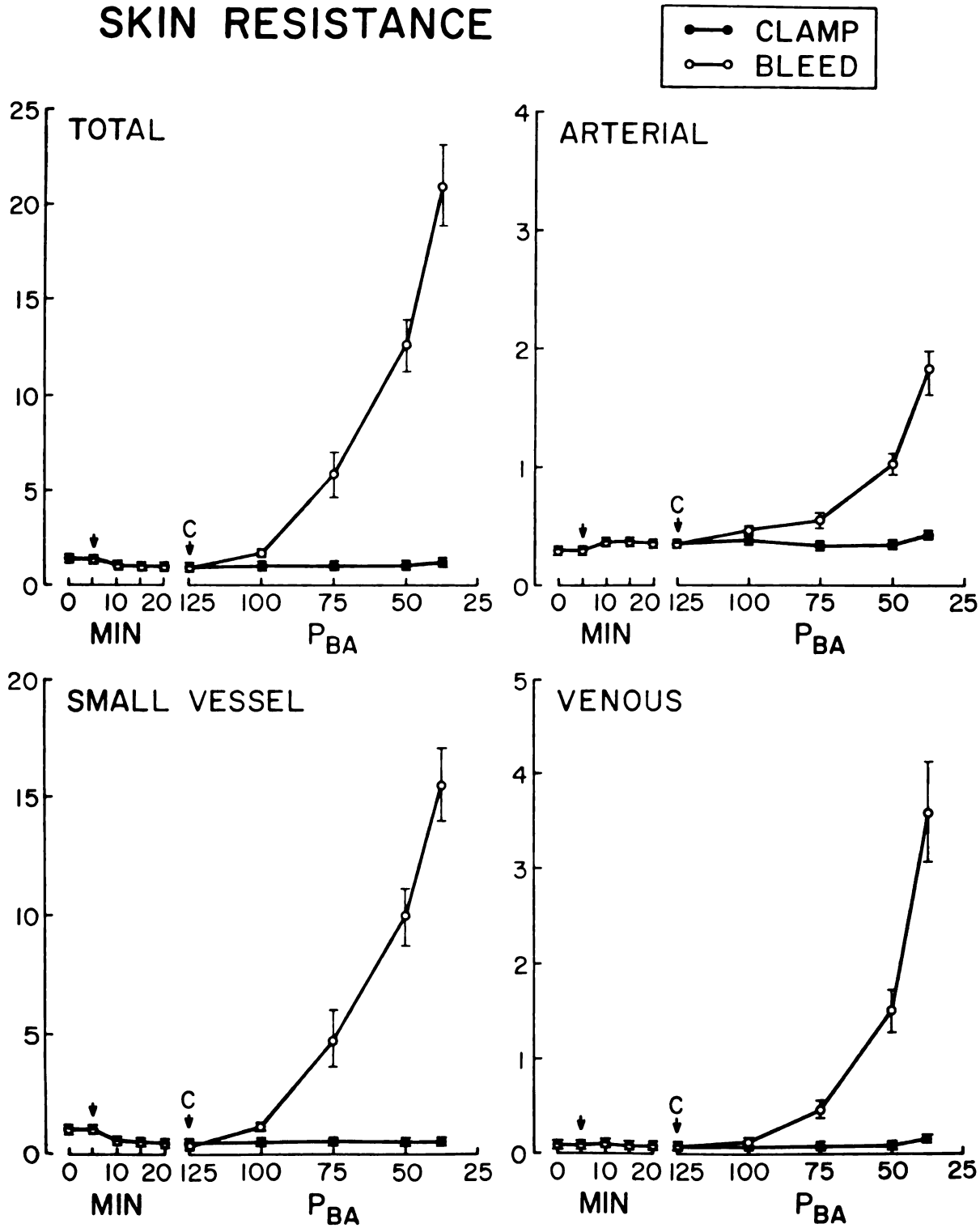

SKIN RESISTANCE
CLAMP
BLEED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
0 10 20 125 100 75 50 25
MIN
P_{BA}

Figure 9

0.94 ± 0.07 20 minutes after denervation. This response, which represents a 33 percent reduction from control resistance, is due primarily to dilation of the small vessel segment in which resistance decreased from 1.01 ± 0.06 before denervation to 0.47 ± 0.03 20 minutes after denervation. Denervation increased skin arterial resistance but did not alter skin venous resistance significantly.

Local hypotension in the forelimb vasculature, produced by clamping the brachial artery, did not elicit significant changes in skin total, arterial, or small vessel resistance. Skin venous resistance was significantly elevated only at a brachial artery pressure of 35 mm Hg, where resistance increased from a control value of 0.09 ± 0.01 to 0.17 ± 0.01.

When forelimb perfusion pressure was lowered by hemorrhage, skin total, small vessel, and venous resistances increased significantly above control at all brachial artery pressures of 100 mm Hg and below. Skin total vascular resistance increased progressively from a control value of 0.88 ± 0.04 to 20.96 ± 2.14 at a brachial artery pressure of 35 mm Hg. Although most of the increase in total skin vascular resistance resulted from constriction of the small vessel segment, the percent increase in resistance was greatest in the skin veins as shown in Table 8. Skin arterial resistance was not significantly increased above control until brachial artery pressure was reduced to 50 mm Hg and below.

Table 8. Effects of local hypotension and rapid arterial hemorrhage on skin total (ST), arterial (SA), small vessel (SSV), and venous (SV) resistances (R) (expressed as percent of control) in denervated forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 17 experiments.

	P_{BA}	R_{ST} %	R_{SA} %	R_{SSV} %	R_{SV} %
Control	114.7	100	100	100	100
Clamp	99.3	107	105	111	97
	76.4	99	89	107	92
	51.0	102	94	106	117
	34.4	120	116	109	197
Control	116.6	100	100	100	100
Bleed	100.0	214	120	317	158
	76.7	663	143	1191	552
	52.9	1423	265	2455	1901
	35.7	2387	465	3824	4533

Figure 10. Effects of rapid arterial hemorrhage on skin vascular resistances in innervated (solid lines; N = 16) or denervated (dashed lines; N = 17) forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-hemorrhage control values. Data represent mean values $\pm$ standard errors.

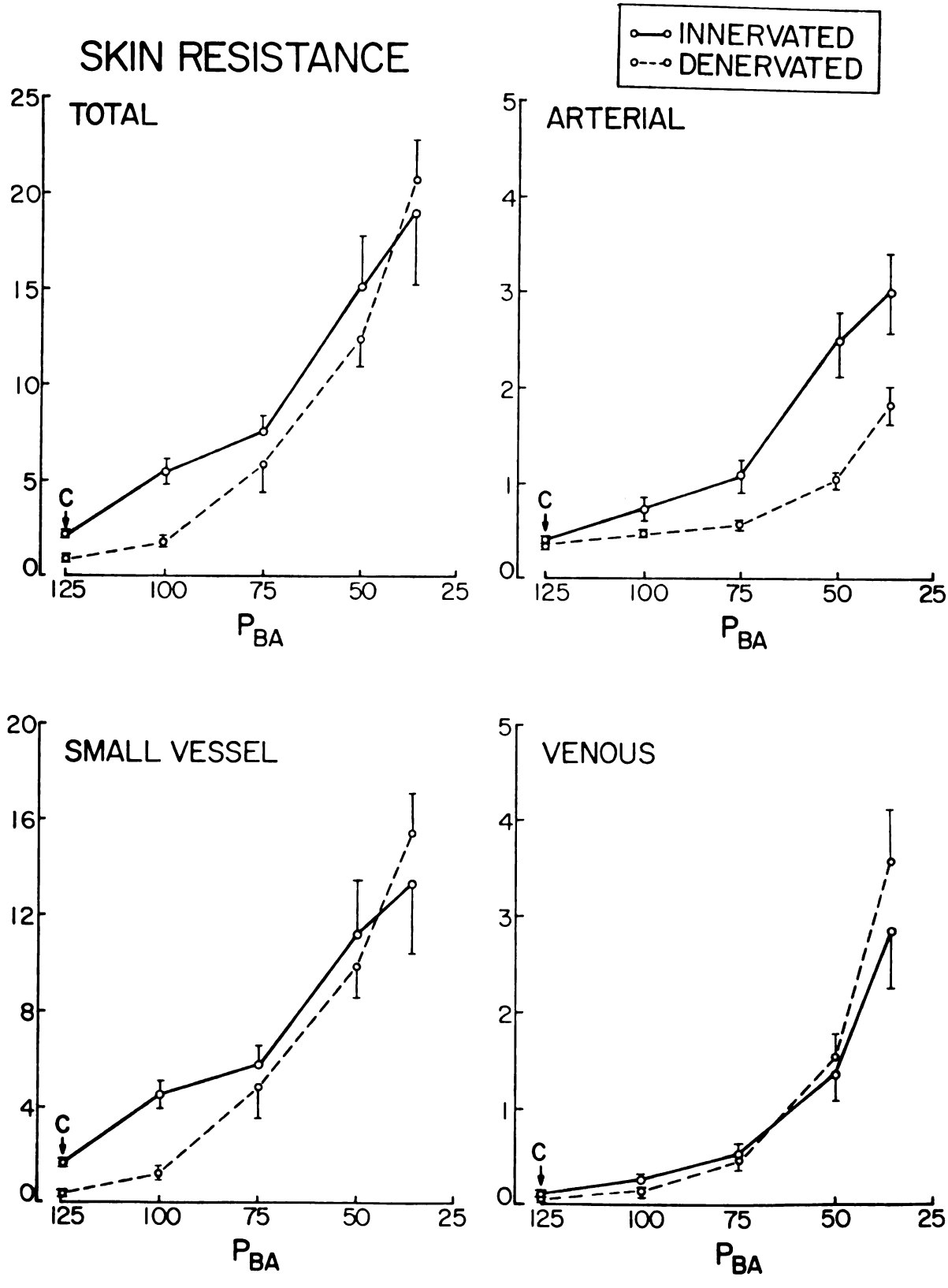

SKIN RESISTANCE
INNERVATED
DENERVATED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
125
100
75
50
25
P_{BA}

Figure 10

A comparison of the responses to bleeding in innervated and denervated skin vascular segments is presented in Figure 10. Data are the same as those reported in Figure 6 (innervated) and 9 (denervated). Resistance was significantly lower in the denervated skin arteries at all brachial artery pressures below control, indicating that denervation attenuates the hemorrhage-induced constrictor response in this vascular segment. Resistance in denervated skin small vessels was significantly lower than in innervated small vessels only at a brachial artery pressure of 100 mm Hg, indicating a slight attenuation of the constrictor response of this vascular segment during moderate hemorrhage. The response of the skin venous segment to bleeding was not significantly reduced by denervation.

D. Muscle Total and Segmental Vascular Resistances

Total and segmental resistances in the muscle vasculature of 17 forelimbs before and after denervation and during hypotension produced by clamping the brachial artery or by arterial hemorrhage are shown in Figure 11. When the forelimb nerves were sectioned (indicated by the first arrow on each graph), total muscle vascular resistance decreased from 2.42 $\pm$ 0.16 before denervation to 1.68 $\pm$ 0.14 20 minutes after denervation. This response, which represents a 31 percent reduction in resting resistance, is due largely to dilation of the small vessel segment, in which resistance

Figure 11. Effects of denervation (first arrow on each graph), local hypotension (solid dots), and rapid arterial hemorrhage (circles) on muscle total, arterial, small vessel, and venous resistances. Ordinates represent resistance in mm Hg(ml/min)$^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg and time in minutes (MIN) after denervation. C = pre-clamp and pre-hemorrhage control values. Data represent means $\pm$ standard errors from 17 experiments.

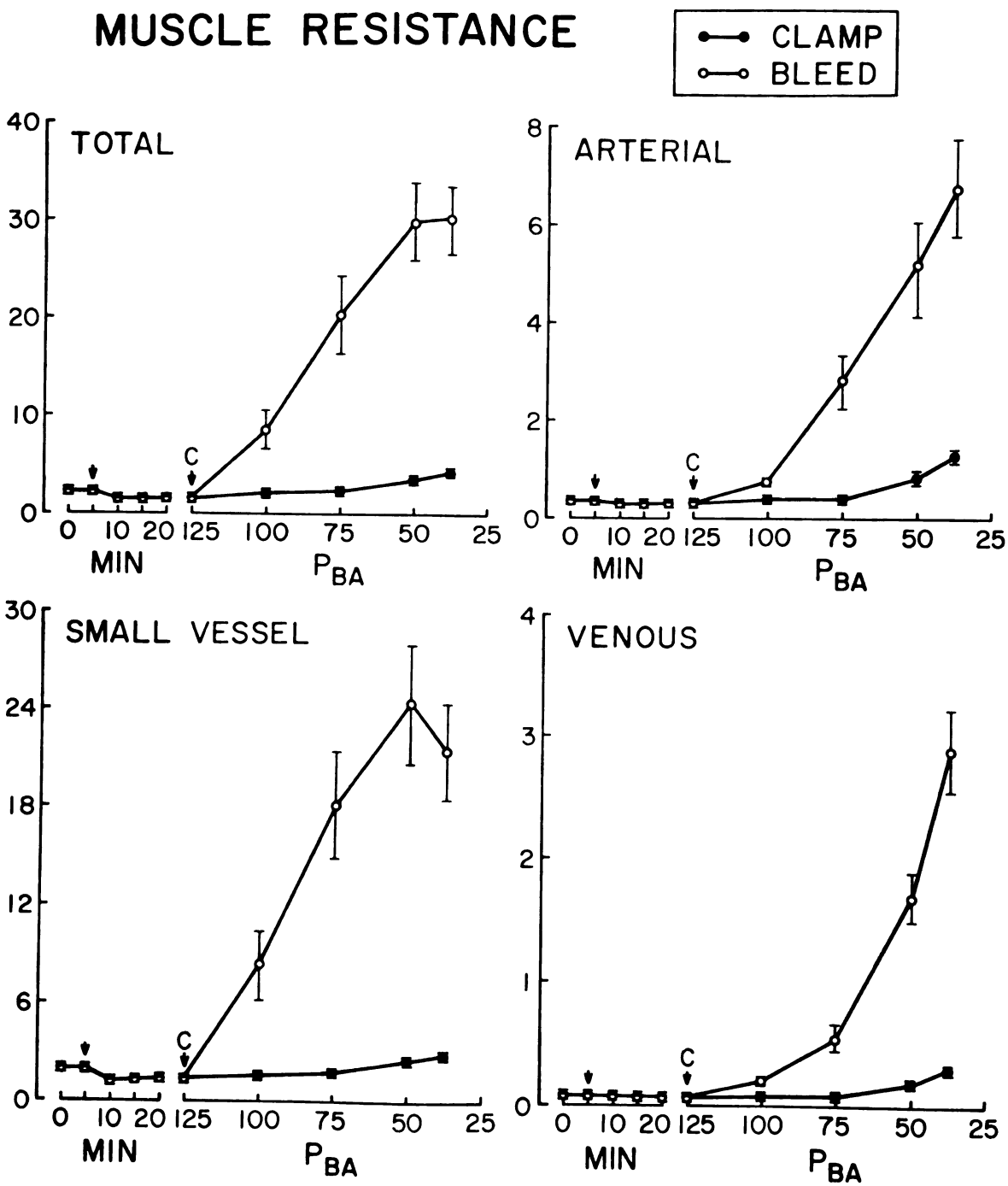

MUSCLE RESISTANCE
CLAMP
BLEED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
0 10 20
MIN
125 100 75 50 25
P_BA

Figure 11

decreased from 2.03 ± 0.13 before denervation to 1.34 ± 0.12 20 minutes after denervation. Denervation produced no significant decreases in muscle arterial or venous resistances.

When forelimb perfusion pressure was lowered by clamping the brachial artery, small but significant increases in muscle arterial and small vessel resistances occurred at brachial artery pressures of 75, 50, and 35 mm Hg. Muscle arterial and small vessel resistance increased from control values of 0.31 ± 0.03 and 1.34 ± 0.12, to 1.34 ± 0.16 and 2.74 ± 0.26 respectively at a brachial artery pressure of 35 mm Hg. Muscle total and venous resistances increased significantly only at brachial artery pressures of 50 and 35 mm Hg.

Arterial hemorrhage elicited significant increases in muscle total and all segmental vascular resistances at brachial artery pressures of 100, 75, 50, and 35 mm Hg. Muscle total resistance increased progressively from a control value of 1.57 ± 0.10 to 30.07 ± 3.62 at brachial artery pressure 35 mm Hg. Although constriction in the small vessel segment accounted for most of the increase in total muscle resistance, the muscle arterial and venous segments constricted proportionately more than the small vessel segment during hemorrhage as shown in Table 9.

A comparison of the results in series I and II (Figure 12) reveals that denervation did not significantly reduce

Table 9. Effects of local hypotension and rapid arterial hemorrhage on muscle total (MT), arterial (MA), small vessel (MSV), and venous (MV) resistances (R) (expressed as percent of control) in denervated forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 17 experiments.

	P_{BA}	R_{MT} %	R_{MA} %	R_{MSV} %	R_{MV} %
Control	114.7	100	100	100	100
Clamp	99.3	127	138	127	112
	76.4	136	135	137	132
	51.0	210	276	193	273
	34.4	255	432	204	442
Control	116.6	100	100	100	100
Bleed	100.0	545	230	683	286
	76.7	1300	848	1500	819
	52.9	1899	1565	2024	2420
	35.5	1915	2036	1775	4130

Figure 12. Effects of rapid arterial hemorrhage on muscle vascular resistances in innervated (solid lines; N = 16) or denervated (dashed lines; N = 17) forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-hemorrhage control values. Data represent mean values $\pm$ standard errors.

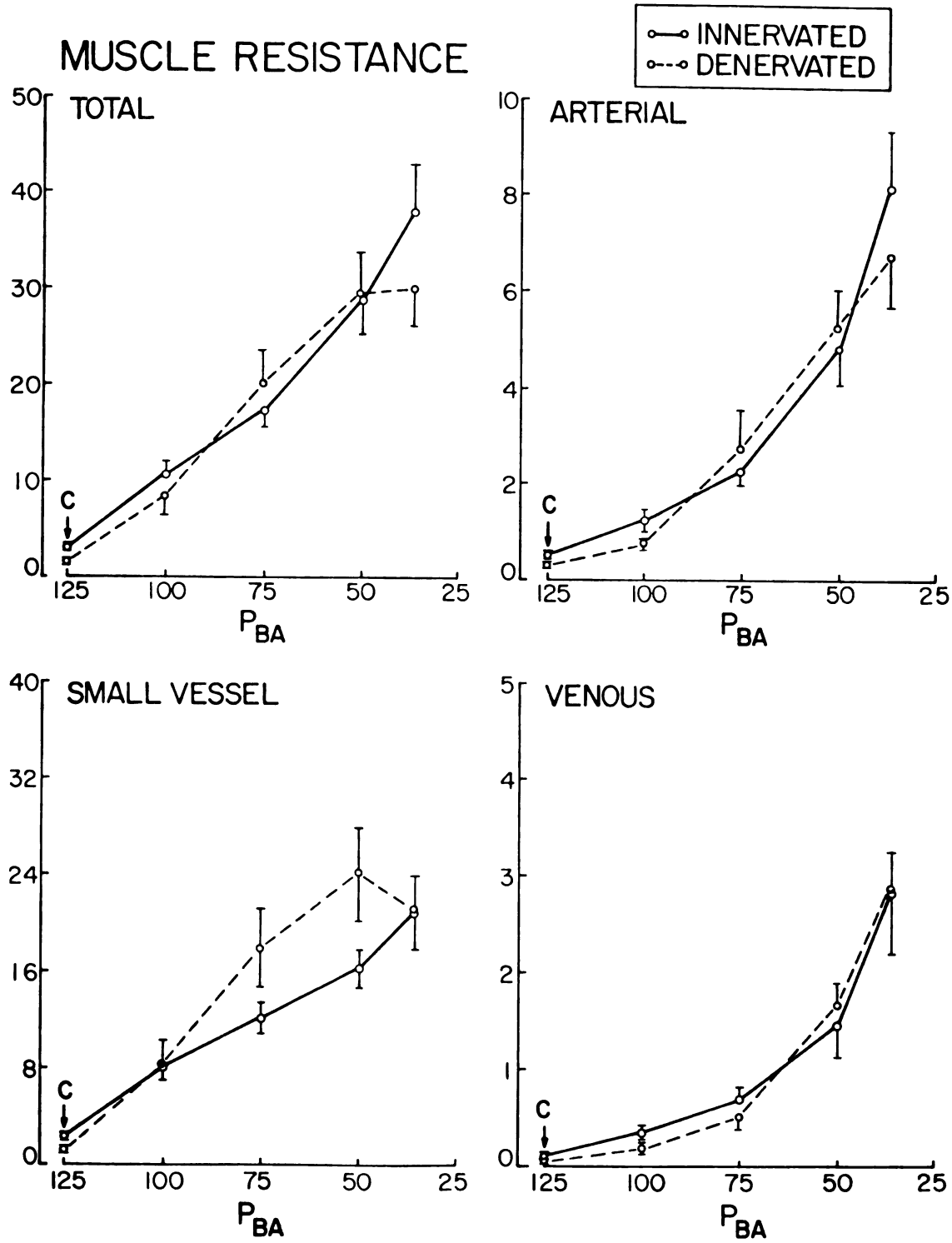

MUSCLE RESISTANCE
INNERVATED
DENERVATED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
125
100
75
50
25
P_{BA}

Figure 12

the resistance response to hemorrhage in the muscle small vessels or veins. Resistance in the denervated muscle large arteries was significantly lower than in the innervated large arteries at a brachial artery pressure of 100 mm Hg; at brachial artery pressures of 75, 50, and 35 mm Hg, resistances in innervated and denervated muscle large arteries were not significantly different.

III. Series III: Cross-perfused Forelimbs; Effects of Rapid Arterial Hemorrhage of the Recipient and Donor Dogs

A. Skin Total and Segmental Vascular Resistances

Bleeding the recipient or donor dogs produced significant increases in skin total and segmental vascular resistances in the forelimbs of the recipient dogs (Figure 13). However, at brachial artery pressures of 75, 50, and 35 mm Hg, hemorrhagic hypotension in the donor dogs elicited a significantly greater increase in skin total and small vessel resistance than did a corresponding degree of hypotension in the recipient dogs. Bleeding the donor dogs to a mean systemic arterial pressure of 35 mm Hg produced a 12.0 fold increase in skin total resistance whereas, hemorrhaging the recipient dogs to a corresponding brachial artery pressure elicited only a 4.2 fold increase in total skin vascular resistance (Table 10). Increases in skin venous resistance at brachial artery pressures of 50 and 35 mm Hg were

Figure 13. Effects of rapid arterial hemorrhage of recipient (solid dots) and donor (circles) dogs on skin total, arterial, small vessel, and venous resistances in cross-perfused forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-hemorrhage control values. Data represents means $\pm$ standard errors from 5 experiments.

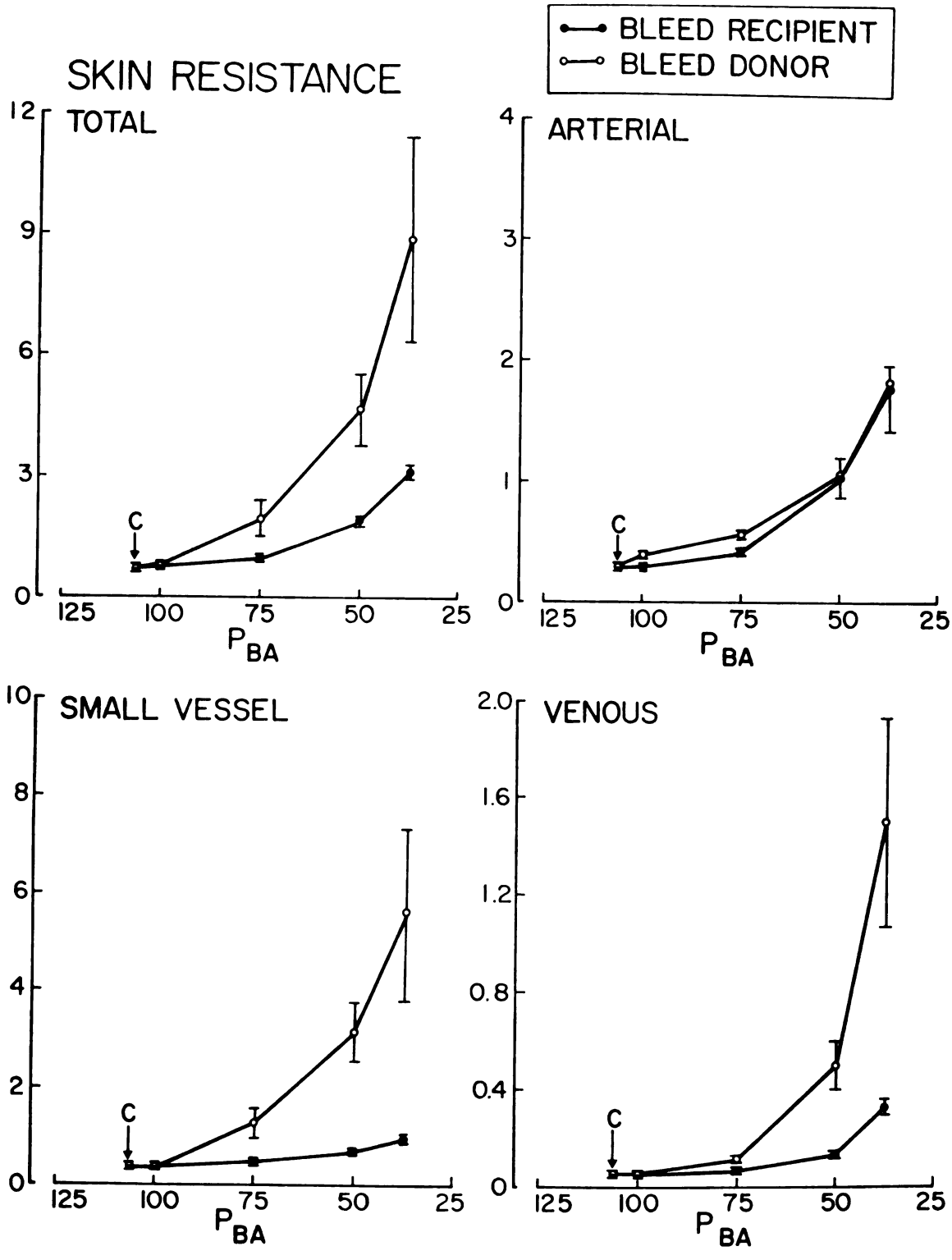

BLEED RECIPIENT
BLEED DONOR
SKIN RESISTANCE
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
125
100
75
50
25
P BA

Figure 13

Table 10. Effects of rapid arterial hemorrhage on skin total (ST), arterial (SA), small vessel (SSV), and venous (SV) resistances (R) (expressed as percent of control) in cross-perfused forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 5 experiments.

	P_{BA}	R_{ST} %	R_{SA} %	R_{SSV} %	R_{SV} %
Control	106.3	100	100	100	100
Bleed Recipient					
	100.0	104	111	98	120
	75.0	132	150	122	140
	50.0	255	368	176	280
	35.4	419	650	229	660
Control	104.7	100	100	100	100
Bleed Donor	100.0	116	124	111	117
	74.8	266	179	360	200
	49.1	635	321	894	833
	34.2	1199	536	1600	2500

significantly greater during hemorrhage of the donor dogs than during bleeding of the recipient dogs. Hemorrhaging the donor or recipient dogs produced no significant differences in the resistance response of the skin arteries.

B. Muscle Total and Segmental Vascular Resistances

Muscle total and all segmental vascular resistances in the forelimbs of the recipient dogs were increased by bleeding the donor or recipient dogs (Figure 14). At brachial artery pressures of 75, 50, and 35 mm Hg, significantly greater increases in muscle total, small vessel, and venous resistances occurred when the donor dogs were bled than when the recipient dogs were bled to corresponding systemic arterial pressures. At a brachial artery pressure of 35 mm Hg, muscle total resistance increased 10.6 fold when the donor dogs were bled, but only 3.4 fold when the recipient dogs were hemorrhaged to a corresponding pressure (Table 11). In muscle arteries, bleeding the donor dogs to arterial pressures of 50 and 35 mm Hg elicited significantly greater increases in resistance than did hemorrhaging the recipient dogs to the same systemic arterial pressures.

Figure 14. Effects of rapid arterial hemorrhage of recipient (solid dots) and donor (circles) dogs on muscle total, arterial, small vessel, and venous resistances in cross-perfused forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent brachial artery pressure (P_{BA}) in mm Hg. C = pre-hemorrhage control values. Data represents means $\pm$ standard errors from 5 experiments.

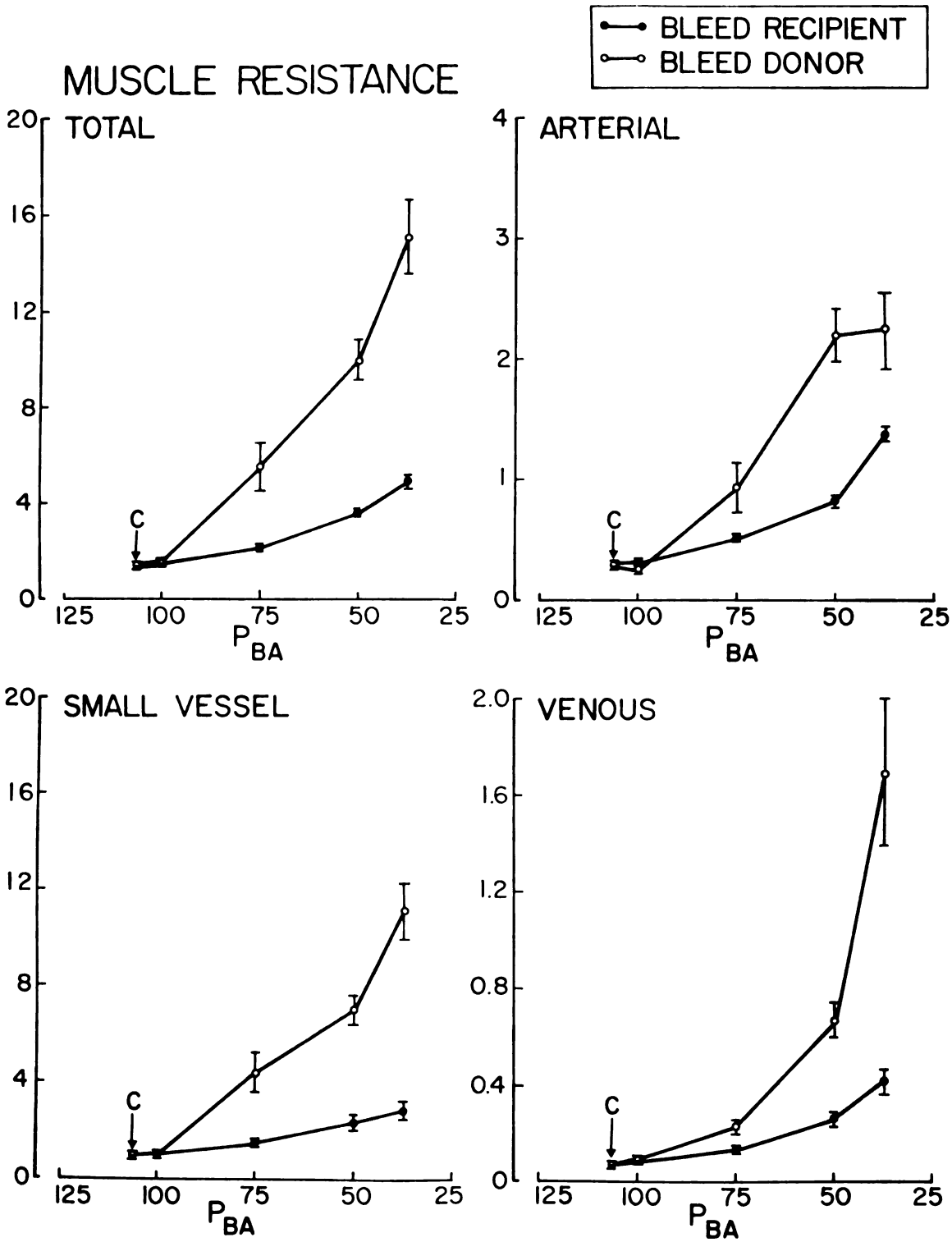

BLEED RECIPIENT
BLEED DONOR
MUSCLE RESISTANCE
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
C
P_{BA}
125
100
75
50
25
0
4
8
12
16
20
1
2
3
0.4
0.8
1.2
1.6
2.0

Figure 14

Table 11. Effects of rapid arterial hemorrhage on muscle total (MT), arterial (MA), small vessel (MSV), and venous (MV) resistances (R) (expressed as percent of control) in cross-perfused forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 5 experiments.

	P_{BA}	R_{MT} %	R_{MA} %	R_{MSV} %	R_{MV} %
Control	106.3	100	100	100	100
Bleed Recipient					
	100.0	106	97	105	100
	75.0	152	158	141	175
	50.0	248	252	223	325
	35.4	340	418	261	525
Control	104.7	100	100	100	100
Bleed Donor	100.0	103	80	108	125
	74.8	392	317	422	288
	49.1	693	733	670	838
	34.2	1057	747	1065	2113

IV. Series IV: Naturally Perfused, Innervated or Denervated Forelimbs; Effects of Slow, Continuous Hemorrhage

A. Mean Arterial Pressure, Pulse Pressure, and Central Venous Pressure

Mean systemic arterial pressure, pulse pressure, and central venous pressures are shown as functions of the total blood loss in ml/kg body weight in Figure 15. The responses of 8 dogs with innervated forelimbs are compared to the responses of 9 dogs with acutely denervated limbs during the removal of 0.41 ml blood/kg body weight per minute. Hemorrhage did not produce a significant change in mean arterial pressure until the cumulative blood loss reached approximately 14.7 mg/kg (after 36 minutes of bleeding) in the dogs with innervated or denervated forelimbs. At the end of the 60 minute bleeding period, when approximately 24.4 ml of blood/kg body weight had been removed, mean arterial pressure was reduced from a control value of 114.7 $\pm$ 2.0 and 115.2 $\pm$ 2.8 to 63.5 $\pm$ 6.5 and 73.4 $\pm$ 5.6 mm Hg in the innervated and denervated groups respectively. Arterial pulse pressure was significantly reduced after removal of approximately 4.9 ml/kg body weight in the innervated and denervated groups, and continued to decrease progressively in both groups throughout the bleeding period. Central venous pressure decreased significantly after a total blood loss of 4.9 ml/kg body weight in the innervated and denervated groups and continued to decrease during hemorrhage.

Figure 15. Effects of slow, continuous hemorrhage on mean systemic arterial, arterial pulse, and central venous pressures in dogs with innervated (solid dots; N = 8) or denervated (circles; N = 9) forelimbs. Ordinates represent pressure in mm Hg and abscissas represent accumulated blood loss in ml/kg body weight. Data represent means $\pm$ standard errors.

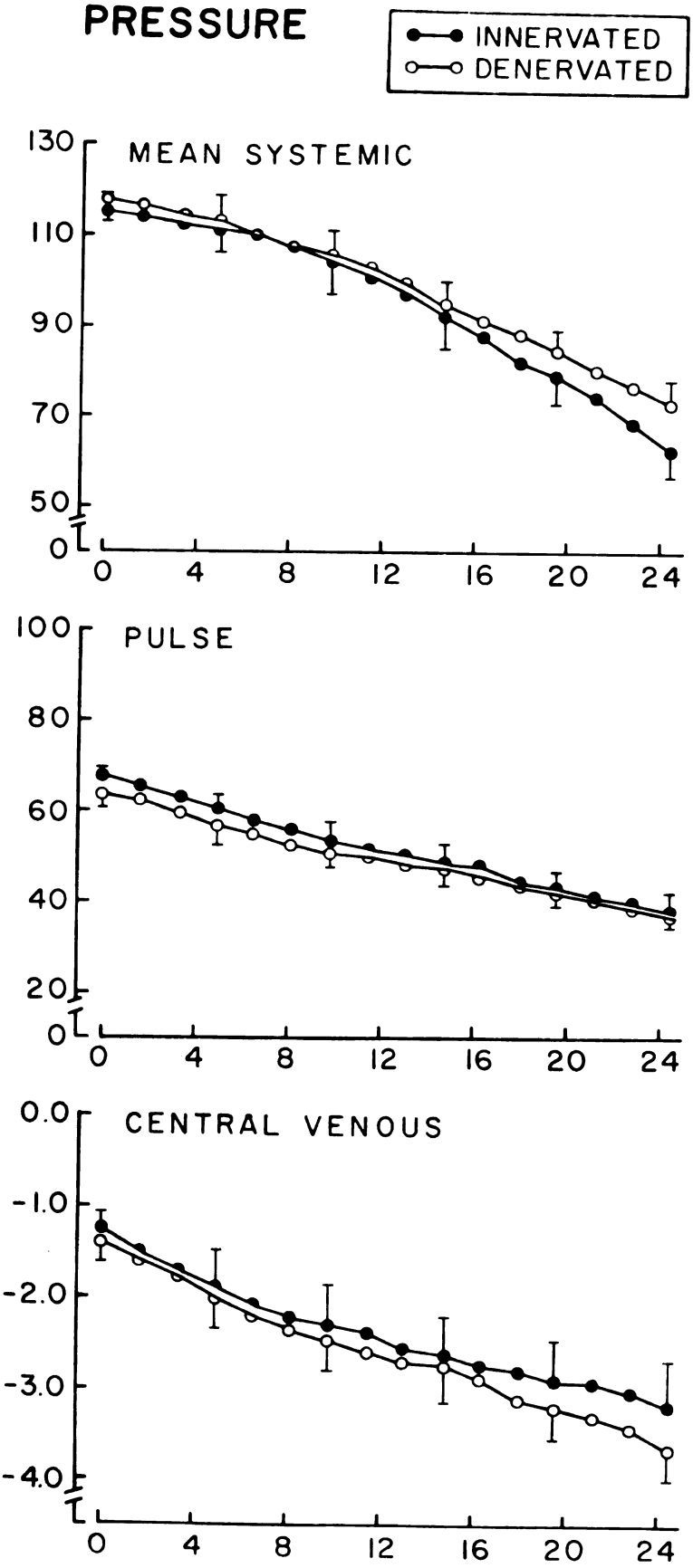

PRESSURE
INNERVATED
DENERVATED
MEAN SYSTEMIC
130
110
90
70
50
0
0
4
8
12
16
20
24
PULSE
100
80
60
40
20
0
0
4
8
12
16
20
24
CENTRAL VENOUS
0.0
-1.0
-2.0
-3.0
-4.0
0
4
8
12
16
20
24

Figure 15

There were no significant differences in mean systemic arterial pressure, arterial pulse pressure, or central venous pressure between the innervated and denervated groups during the control period or during the hemorrhage period, suggesting that both groups were subjected to similar bleeding stresses.

B. Skin Total and Segmental Vascular Resistances

Data in Figure 16 illustrate the resistance response in the skin vasculature of 8 innervated and 9 denervated forelimbs in animals subjected to a blood loss of 0.41 ml/kg body weight per minute. Hemorrhage produced significant increases in skin total, arterial, small vessel, and venous resistances in both innervated and denervated forelimbs. A marked and progressive constriction was observed in all innervated skin segments, and total skin resistance increased from a control value of 1.38 $\pm$ 0.12 to 9.25 $\pm$ 2.85 after 60 minutes of bleeding (or after approximately 24.4 ml blood loss per kg body weight). However, the constriction in all denervated skin vascular segments was small, with total skin resistance increasing from a control value of 0.81 $\pm$ 0.05 to 1.49 $\pm$ 0.19 after 60 minutes of hemorrhage. The increases in skin total and small vessel resistances were significantly greater in innervated than denervated forelimbs after removal of approximately 5 ml blood/kg body weight (12 minutes of bleeding). The increase in skin

Figure 16. Effects of slow, continuous hemorrhage on skin total, arterial, small vessel, and venous resistances in innervated (solid dots; N = 8) or denervated (circles; N = 9) forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent accumulated blood loss in ml/kg body weight. Data represent means $\pm$ standard errors.

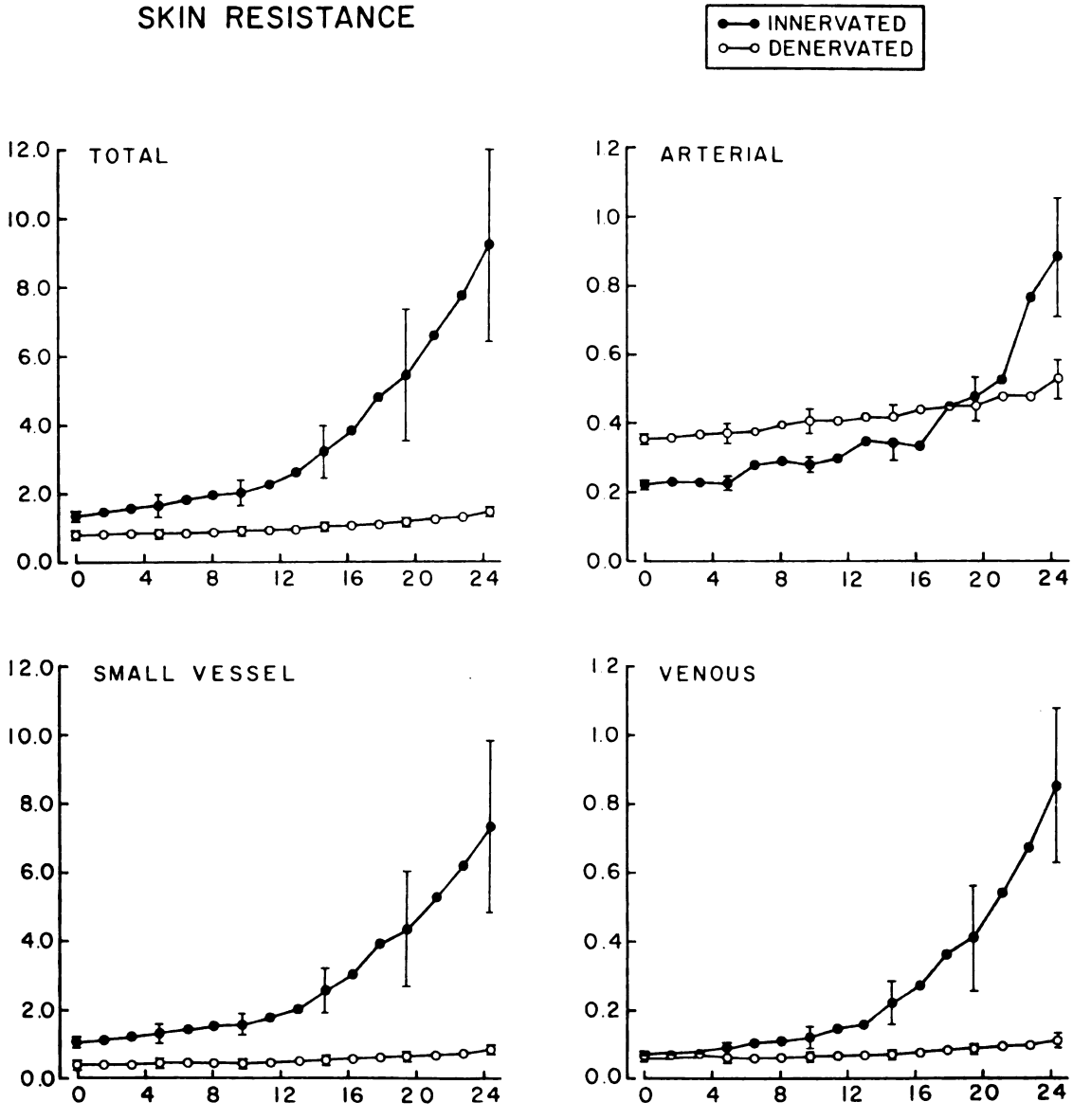

SKIN RESISTANCE
INNERVATED
DENERVATED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24

Figure 16

Table 12. Effects of slow, continuous hemorrhage on skin total (ST), arterial (SA), small vessel (SSV), and venous (SV) resistances (R) (expressed as percent of control) in innervated forelimbs. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means ± standard errors from 8 experiments.

MIN	R_{ST}	R_{SA}	R_{SSV}	R_{SV}	Blood Loss
0	100	100	100	100	0.00
2	106± 2	107± 4	106± 3	105± 2	0.81
4	107± 3	104± 5	108± 4	110± 5	1.63
6	110± 4	103± 4	112± 5	113± 6	2.44
8	114± 4	103± 2	116± 5	119± 7	3.20
10	119± 5	107± 3	123± 7	119± 8	4.07
12	123± 6	101± 6	129± 8	125± 11	4.88
14	127± 6	110± 8	132± 7	133± 15	5.70
16	134± 7	125±12	137± 8	149± 17	6.51
18	139± 8	126±10	141± 9	157± 21	7.33
20	144± 8	132±15	147± 10	162± 25	8.14
22	144± 9	124± 9	148± 11	164± 23	8.95
24	147± 9	126± 5	150± 11	173± 24	9.77
26	152± 11	128± 9	157± 14	183± 29	10.58
28	163± 15	135±13	169± 19	201± 36	11.40
30	175± 18	141±12	181± 23	213± 39	12.21
32	179± 21	157±18	183± 24	218± 38	13.02
34	209± 37	162±17	219± 46	272± 58	13.84
36	231± 53	160±27	248± 66	301± 76	14.65
38	245± 57	174±21	262± 71	318± 84	15.47
40	287± 81	153±25	321±106	386±121	16.28
42	352±142	153±25	401±182	486±186	17.09
44	382±153	203±34	425±193	522±193	17.91
46	389±152	216±36	431±192	540±193	18.72
48	424±180	211±28	476±226	592±231	19.54
50	469±184	249±47	519±231	699±246	20.35
52	526±202	238±39	592±249	852±310	21.16
54	588±208	326±78	641±258	985±347	21.98
56	653±239	344±64	717±291	1156±411	22.79
58	699±253	364±77	768±316	1270±448	23.61
60	763±277	393±69	841±340	1458±511	24.42

Table 13. Effects of slow, continuous hemorrhage on skin total (ST), arterial (SA), small vessel (SSV), and venous (SV) resistances (R) (expressed as percent of control) in denervated forelimbs. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means ± standard errors from 9 experiments.

MIN	R_{ST}	R_{SA}	R_{SSV}	R_{SV}	Blood Loss
0	100	100	100	100	0.00
2	100± 1	101± 1	100± 2	103± 2	0.81
4	100± 1	100± 1	101± 2	102± 2	1.03
6	103± 2	102± 1	104± 3	105± 1	2.44
8	105± 2	104± 1	107± 3	105± 1	3.20
10	105± 2	104± 1	107± 3	105± 2	4.07
12	106± 3	105± 1	108± 4	103± 2	4.88
14	105± 3	106± 2	109± 4	105± 1	5.70
16	109± 3	106± 2	114± 5	105± 2	6.51
18	111± 3	109± 2	115± 6	111± 4	7.33
20	113± 3	112± 2	117± 7	111± 3	8.14
22	113± 4	111± 4	120± 8	108± 3	8.95
24	116± 4	116± 5	119± 7	109± 3	9.77
26	116± 4	117± 6	120± 8	113± 4	10.58
28	118± 4	116± 7	124± 9	114± 4	11.40
30	120± 4	117± 7	128± 9	111± 4	12.21
32	122± 4	118± 8	132± 9	110± 6	13.02
34	123± 5	119± 7	134±10	112± 5	13.84
36	127± 4	119± 8	142±11	115± 6	14.65
38	131± 4	123± 8	146±11	116± 7	15.47
40	134± 5	125± 9	150±11	119± 8	16.28
42	139± 5	127±10	158±12	118± 8	17.09
44	142± 6	129±10	163±13	120±10	17.91
46	147± 8	131± 9	170±13	138±12	18.72
48	149± 9	127± 6	178±15	136±14	19.54
50	155±10	126± 6	193±21	142±16	20.35
52	158±12	136± 7	189±22	148±19	21.16
54	164±14	139±12	198±29	148±21	21.98
56	167±15	134±12	210±34	159±24	22.79
58	180±21	143±12	228±43	172±34	23.61
60	193±31	152±12	244±53	196±52	24.42

arterial resistance was significantly greater in the innervated limbs only after the cumulative blood loss had reached about 20 ml/kg body weight (48 minutes of bleeding). Resistance in innervated skin veins exceeded that in denervated skin veins after the accumulated blood loss was approximately 10 ml/kg body weight (24 minutes of bleeding). In the innervated skin vasculature, although small vessel constriction produced most of the rise in total skin resistance, the skin veins constricted proportionately more than the small vessels as shown in Table 12. In the denervated forelimbs, small vessels constricted proportionately more than any other skin vascular segment during hemorrhage as shown in Table 13.

C. Muscle Total and Segmental Vascular Resistances

Total and segmental resistances in the muscle vasculature of 8 innervated and 9 denervated forelimbs during slow hemorrhage are presented in Figure 17. Muscle total and all segmental vascular resistances in both innervated and denervated forelimbs increased significantly during hemorrhage. However, a more pronounced increase in muscle total, small vessel, and venous resistance occurred in innervated than in denervated forelimbs. In the innervated limbs, muscle total resistance increased from 2.20 $\pm$ 0.13 during the control period to 11.01 $\pm$ 1.85 after 60 minutes of bleeding. Total muscle vascular resistance in the denervated

Figure 17. Effects of slow, continuous hemorrhage on muscle total, arterial, small vessel, and venous resistances in innervated (solid dots; N = 8) or denervated (circles; N = 9) forelimbs. Ordinates represent resistance in mm Hg $(ml/min)^{-1}$ and abscissas represent accumulated blood loss in ml/kg body weight. Data represent means $\pm$ standard errors.

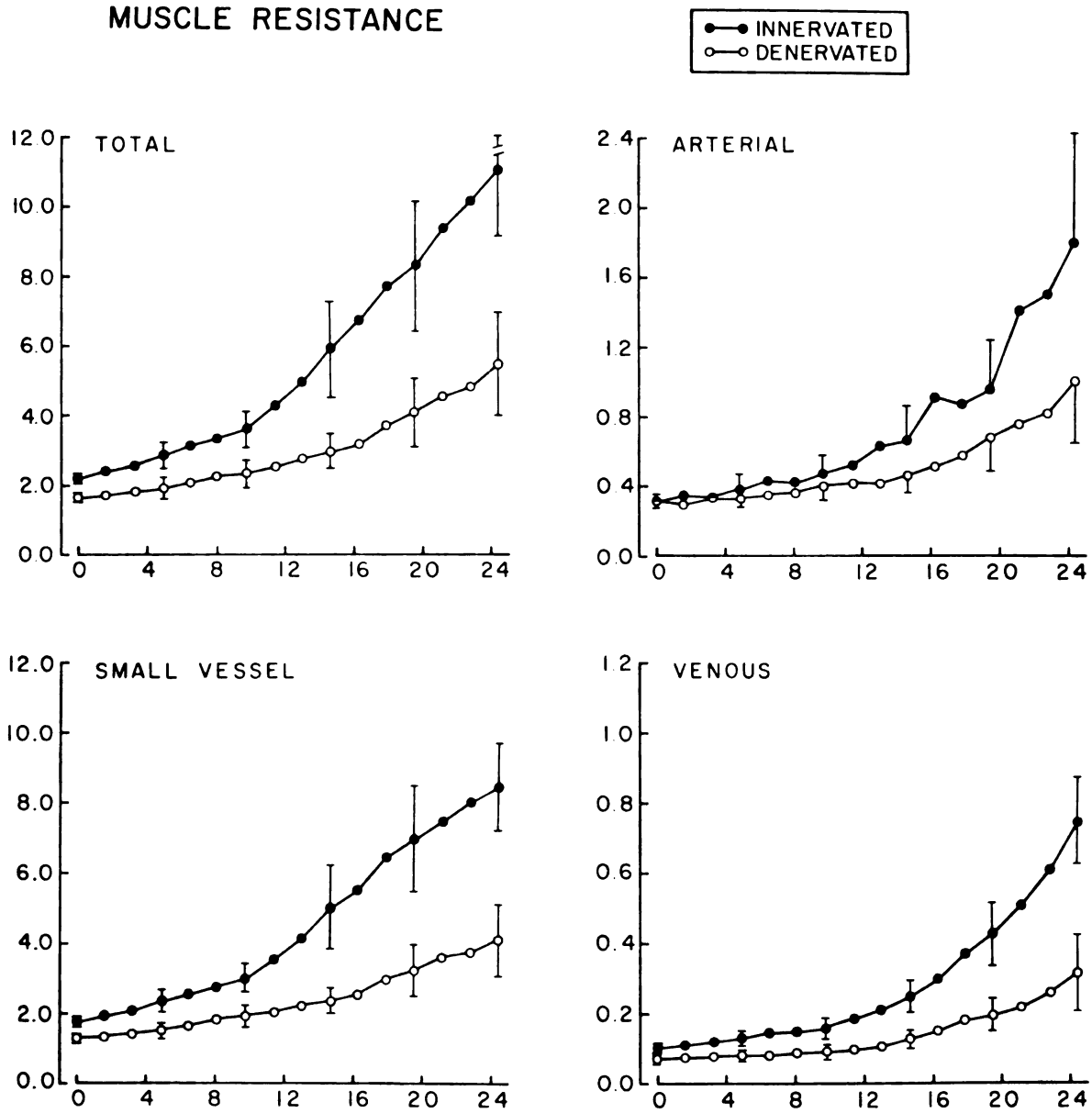

MUSCLE RESISTANCE
INNERVATED
DENERVATED
TOTAL
ARTERIAL
SMALL VESSEL
VENOUS
12.0
10.0
8.0
6.0
4.0
2.0
0.0
2.4
2.0
1.6
1.2
0.8
0.4
1.2
1.0
0.8
0.6
0.4
0.2
0
4
8
12
16
20
24

Figure 17

Table 14. Effects of slow, continuous hemorrhage on muscle total (MT), arterial (MA), small vessel (MSV), and venous (MV) resistances (R) (expressed as percent of control) in innervated forelimbs. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means ± standard errors from 8 experiments.

MIN	R_{MT}	R_{MA}	R_{MSV}	R_{MV}	Blood Loss
0	100	100	100	100	0.00
2	106± 1	117± 10	105± 2	104± 4	0.81
4	106± 2	108± 10	106± 2	108± 6	1.63
6	110± 4	117± 7	109± 4	112± 8	2.44
8	114± 4	104± 8	116± 6	117± 8	3.20
10	122± 6	113± 4	124± 6	125± 10	4.07
12	127± 8	115± 6	130± 9	132± 13	4.88
14	131± 7	106± 8	136± 8	137± 14	5.70
16	141±10	145± 20	143±11	147± 15	6.51
18	147±12	141± 14	150±13	156± 18	7.33
20	149±12	140± 19	154±14	155± 21	8.14
22	157±15	133± 5	162±17	159± 23	8.95
24	162±15	143± 8	166±16	166± 24	9.77
26	169±15	151± 9	174±17	178± 23	10.58
28	187±19	158± 11	194±22	193± 30	11.40
30	190±22	154± 10	200±26	201± 34	12.21
32	198±26	170± 22	204±27	212± 48	13.02
34	212±31	197± 24	217±33	247± 66	13.84
36	231±34	183± 28	243±28	264± 62	14.65
38	240±30	211± 27	248±32	275± 65	15.47
40	264±36	198± 30	277±35	309± 72	16.28
42	303±54	247± 50	317±57	369± 97	17.09
44	318±51	261± 41	332±57	371±100	17.91
46	330±48	272± 38	339±53	407± 94	18.72
48	344±53	259± 37	359±57	430±102	19.54
50	384±62	303± 46	398±66	485±107	20.35
52	410±63	294± 82	424±64	526±115	21.16
54	442±68	380± 78	423±71	604±128	21.98
56	481±81	420± 99	483±84	655±137	22.79
58	511±91	444±112	508±93	744±171	23.61
60	528±89	466±136	518±90	802±181	24.42

Table 15. Effects of slow, continuous hemorrhage on muscle total (MT), arterial (MA), small vessel (MSV), and venous (MV) resistances (R) (expressed as percent of control) in denervated forelimbs. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means ± standard errors from 9 experiments.

MIN	R_{MT}	R_{MA}	R_{MSV}	R_{MV}	Blood Loss
0	100	100	100	100	0.00
2	101± 1	96± 4	102± 1	105± 4	0.81
4	102± 1	94± 5	103± 2	107± 5	1.63
6	106± 2	101±14	107± 3	107± 7	2.44
8	109± 3	101± 5	112± 4	106± 4	3.20
10	112± 5	103± 6	115± 5	106± 4	4.07
12	115± 4	105± 6	118± 5	110± 5	4.88
14	120± 5	109± 8	123± 6	124± 6	5.70
16	123± 6	108±11	128± 6	118± 10	6.51
18	126± 7	106±11	131± 7	121± 9	7.33
20	132±10	109±14	138±11	132± 11	8.14
22	136±11	115±13	143±11	131± 11	8.95
24	139± 9	122±11	144±10	133± 13	9.77
26	142±10	119±13	148±10	136± 14	10.58
28	149±10	124±15	156±10	137± 16	11.40
30	159±15	123±22	169±14	147± 16	12.21
32	160±14	123±18	169±14	153± 21	13.02
34	161±13	138±19	167±12	175± 35	13.84
36	173±16	140±20	181±15	187± 35	14.65
38	178±16	146±21	185±14	196± 38	15.47
40	187±17	152±22	194±16	210± 38	16.28
42	196±22	160±26	203±21	226± 47	17.09
44	213±27	166±32	223±26	247± 52	17.91
46	219±30	191±36	223±29	246± 51	18.72
48	231±37	196±39	237±36	267± 62	19.54
50	245±43	207±44	252±42	288± 68	20.35
52	256±49	219±45	262±49	301± 85	21.16
54	259±47	255±53	257±44	325± 91	21.98
56	269±46	231±54	274±44	353± 91	22.79
58	287±54	284±70	283±48	400±117	23.61
60	304±59	296±78	300±52	428±132	24.42

limbs increased from a control value of 1.66 ± 0.10 to 5.48 ± 1.47 after 60 minutes of bleeding. The increases in muscle total and small vessel resistance were significantly greater in the innervated than in the denervated limbs after a cumulative blood loss of 15 ml/kg body weight (36 minutes of bleeding). The increases in muscle venous resistance were significantly greater in the innervated limbs after removal of 20 ml blood/kg body weight (48 minutes of bleeding). However, the increases in muscle arterial resistance were not statistically different in the innervated and denervated limbs. The resistance responses of the muscle vasculature in innervated and denervated forelimbs during hemorrhage are shown in Tables 14 and 15 as percent of control resistance. In the innervated forelimbs, the veins constricted proportionately more than any other muscle vascular segment. However, in the denervated forelimbs, vascular resistance in arteries, small vessels, and veins increased almost proportionately.

DISCUSSION

I. Series I: Naturally Perfused, Innervated Forelimbs; Local Hypotension and Rapid Arterial Hemorrhage

A. Forelimb Weight

In the present study, slow, sustained changes in forelimb weight were attributed to net transcapillary fluid movement. Since intravascular pressures, venous outflows, and vascular resistances had stabilized before the slow phases of weight loss were measured, it was assumed that changes in vascular capacity did not contribute to this portion of the weight loss.

The rate of extravascular fluid reabsorption during hemorrhage varied between 0.30 ± 0.03 g/min (at a brachial artery pressure of 100 mm Hg) and 0.42 ± 0.03 g/min (at a brachial artery pressure of 75 mm Hg) (Figure 5). Since total forelimb weight averaged 529.1 ± 29.6, with bone comprising approximately 38 percent (82), the combined weight of forelimb skin and skeletal muscle averaged about 325 g. Therefore, the reabsorption rate in soft tissues (primarily skin and skeletal muscle) during hemorrhage averaged between 0.09 and 0.13 g/min per 100 g. Because skin and skeletal muscle comprise about 55 percent of the total body weight

(121), a 15 kg dog subjected to severe hemorrhage might be expected to reabsorb 8-12 g of fluid per minute from these tissues alone. However, quantifications of this type are somewhat hazardous since skin and muscle vascular responses in other parts of the dog may not mimic those in the forelimb. Estimates of the total volume of plasma replaced over several minutes by reabsorption of extravascular fluid in skin and skeletal muscle are further complicated because the amount of extravascular fluid which can be mobilized is limited. In addition, continuous dilution of plasma proteins along with a gradual increase in tissue colloid osmotic pressure will progressively decrease the rate of fluid reabsorption. Estimates of the total contribution made by skin and muscle to the restoration of plasma volume are therefore difficult. However, data reported in this thesis demonstrate that the rate of fluid reabsorption in skin and skeletal muscle is large enough to cause a significant replacement of plasma volume following hemorrhage.

Our findings support those of other investigators (66, 89,98,115) who reported that reabsorption of extravascular fluid in skin and skeletal muscle is important in restoring plasma volume during the early stages of hemorrhagic hypotension. The rate of fluid reabsorption in the present study closely approximates that reported for cat skeletal muscle during the early stages (first 10-15 minutes) of "moderate" or "severe" hemorrhage (rapid removal of 15-40 percent of

the total blood volume) (89). However, some investigators (89,93,96) have reported that fluid reabsorption is not maintained during prolonged hemorrhage. According to Lungren et al. (89), after 20-25 minutes of hypotension, fluid reabsorption in cat skeletal muscle is replaced by net filtration. They attributed the gradual decrease in the rate of fluid reabsorption to a fall in the pre- to post-capillary resistance ratio which allegedly occurred because local regulatory mechanisms selectively dilated precapillary vessels while postcapillary vessels remained constricted. However, Schwinghamer et al. (115) and Grega et al. (66) reported that fluid reabsorption and constriction of pre-capillary vessels are sustained for at least 4 hours during severe hemorrhage (removal of 25-60 percent of the total blood volume). In the present study, the rate of fluid reabsorption was well maintained throughout each of the 20-30 minute periods of hypovolemia (a total of about 80-120 minutes of bleeding) and resistance in all vascular segments of skin and skeletal muscle increased progressively as blood losses increased. Differences between the observations of Lungren et al. and those in the present study, as well as those of Schwinghamer et al. and Grega et al., may be related to differences in species (cats vs. dogs), anesthetic (chloralose-urethane vs. sodium pentobarbital), or experimental design. It is important to note that Lungren et al. held venous pressure constant during hemorrhage. Perhaps

when venous pressure is permitted to fall, as it normally does during hemorrhage, transcapillary fluid absorption is maintained because of a greater, more sustained fall in capillary hydrostatic pressure.

The hemorrhage-induced reabsorption of extravascular fluid could be due to a reduced transcapillary hydrostatic gradient or to an increased transcapillary osmotic gradient (see equation 3). Järhult (80,81) reported that an increased arteriovenous plasma osmolarity gradient (and presumably an increased transcapillary osmolarity gradient) mediates a small but significant portion of the extravascular fluid reabsorption in skeletal muscle during hemorrhage. Plasma osmolarity was not measured in the present study but other investigators (66,115) have reported only small changes in plasma osmolarity in the dog during severe hemorrhage. Therefore, it is unlikely that the rapid rates of fluid reabsorption observed in the present study were due primarily to increases in the transcapillary osmotic gradient. Instead, most of the net transcapillary fluid reabsorption probably resulted from reductions in the net transcapillary hydrostatic gradient due to a fall in capillary pressure.

Capillary hydrostatic pressure could fall because of increases in the pre- to postcapillary resistance ratio and/or decreases in arterial and venous pressures (see equation 4). The slow, sustained weight losses observed when the brachial artery was clamped indicate that reducing

arterial and venous pressures produces significant fluid reabsorption. However, the rate of fluid reabsorption during local hypotension (produced by clamping the brachial artery) was always much less than that observed during hemorrhage even though arterial and venous pressures were reduced to corresponding levels (Figure 5). Therefore, the net fluid reabsorption elicited by hemorrhage is not due primarily to reductions in arterial and venous pressures, but is due largely to a greater pre- to postcapillary resistance ratio and/or an increased capillary filtration coefficient (CFC). Since adrenergic nerves and circulating vasoconstrictors (i.e., catecholamines, angiotensin, vasopressin) which are activated or released during hemorrhage constrict precapillary sphincters and reduce the capillary surface area available for exchange (9,33,98), it is unlikely that CFC is actually higher during hemorrhage than during local hypotension. Therefore, differences in the rate of fluid reabsorption during clamping and bleeding are probably due to differences in the pre- to postcapillary resistance ratio.

The initial, rapid phase of forelimb weight loss, associated with reductions in intravascular capacity, was consistently greater during hemorrhage than during local hypotension (Figure 4). Since bleeding and clamping to corresponding brachial artery pressures did not produce appreciably different mean intraluminal pressures, the larger

reductions in vascular capacity during hemorrhage resulted from active venous constriction. This conclusion is supported by the resistance data (Figures 6 and 7) which indicate that hemorrhage elicits a much larger increase in venous resistance than does a corresponding degree of local hypotension.

Data from the present study do not permit accurate quantification of the amount of blood mobilized from the skin and muscle vasculature due to active and passive venous constriction. However, these data do support those of Lungren et al. (89) and Öberg (98) who concluded that most of the vascular volume reduction in skin and skeletal muscle during hemorrhage could be attributed to active constriction of capacitance vessels.

B. Forelimb Vascular Resistances

Local hypotension elicited slight increases in forelimb vascular resistances. In skin, significant passive constriction occurred only in the large veins. In skeletal muscle, total and segmental resistances increase significantly, but these changes were small and occurred only at brachial artery pressures of 75, 50, and 35 mm Hg. These data suggest that local reductions in arterial and venous pressures do not elicit large decreases in the radii of forelimb vessels.

During hemorrhage, resistance in forelimb vascular segments increased progressively as brachial artery pressure

was reduced to 100 mm Hg and below. The resistance increases observed during hemorrhage were always significantly greater than those produced by clamping to corresponding perfusion pressures. At a brachial artery pressure of 35 mm Hg, total vascular resistances in skin and skeletal muscle increased 9 and 12 fold, respectively, during hemorrhage, whereas, during local hypotension total vascular resistance in skeletal muscle increased only 2 fold and total skin vascular resistance did not increase significantly. These data clearly indicate that the hemorrhage-induced constriction of all vascular segments in skin and skeletal muscle, including the large veins, results primarily from active smooth muscle contraction rather than from passive vascular collapse. The resistance data for arteries and small vessels agree with those of several other investigators (89,66,115). However, hemorrhage-induced increases in venous resistance have been reported by Lesh and Rothe (87) and Haddy et al. (75) to occur primarily because of passive vascular collapse subsequent to a reduced venous transmural pressure. Lesh and Rothe did not calculate large vein resistance, but based their conclusions on observations of changes in muscle weight (see Section II-B of Literature Review). Haddy et al., using a dog forelimb preparation perfused at constant flow, failed to observe an increase in large vein resistance when the dogs were hemorrhaged approximately 21 percent of their total blood volume. In the present study, large vein resistances

were calculated during natural flow conditions, thus avoiding the use of a pump (required for constant flow studies) which may alter vascular reactivity (49). Differences between Haddy et al.'s observations and those in the present study may therefore be related to differences in the method of forelimb perfusion. Other investigators (76,89,98) using natural flow preparations have reported that venous constriction during hemorrhage results partly from active smooth muscle contraction.

II. Series II: Naturally Perfused, Denervated Forelimbs; Local Hypotension and Rapid Arterial Hemorrhage

A. Forelimb Weight

In the denervated forelimbs, both local and hemorrhagic hypotension caused a substantial reabsorption of extravascular fluid as evidenced by the slow, sustained limb weight losses observed during clamping and bleeding (Figure 8). At forelimb perfusion pressures of 100 and 75 mm Hg, hemorrhage elicited a significantly greater rate of fluid reabsorption than did local hypotension, suggesting that the pre- to postcapillary resistance ratio was higher in the skin and muscle vasculature during hemorrhage. This conclusion is based on an analysis of equations 3 and 4 and the assumption that the capillary filtration coefficient during local hypotension was at least as great as during hemorrhage (see Discussion I-A).

The observation that clamping or bleeding to brachial artery pressures of 50 and 35 mm Hg elicited the same rates of weight loss in denervated forelimbs could be explained by either of the following hypotheses: 1) Pre- to post-capillary resistance ratios and CFC's in the denervated forelimbs were not different during local hypotension and hemorrhage. 2) Forelimb pre- to postcapillary resistance ratio is greater during hemorrhage, but CFC is higher during local hypotension. Hypothesis 2 is more plausible since circulating vasoconstrictors, which are released during hemorrhage (i.e., catecholamines, angiotensin, vasopressin), contract precapillary sphincters and thereby decrease the functional capillary surface area (9,51,92,95). This conclusion is supported by the finding that in skeletal muscle, CFC is higher during local hypotension than during hemorrhage (98).

There were no significant differences between the rates of slow, sustained limb weight loss in innervated (Series I) and denervated (Series II) forelimbs during hemorrhage to corresponding brachial artery pressures (Table 5). These data suggest that circulating vasoconstrictors, as well as reductions in arterial and venous pressures, are responsible for most of the extravascular fluid reabsorption in skin and skeletal muscle during rapid arterial hemorrhage, with sympathetic nerves apparently contributing little to this response. These observations differ from those of Öberg (98) who reported that denervation abolished the hemorrhage-induced

reabsorption of extravascular fluid in cat skin and skeletal muscle. An explanation for the differences between Öberg's findings and those in the present study is not apparent, but may be related to differences in animal species (cats vs. dogs) or anesthesia used (chloralose vs. sodium pentobarbital). Critical analysis of Öberg's report is complicated by the fact that all data presented were from single "typical" experiments.

B. Forelimb Vascular Resistances

Local hypotension, produced by clamping the brachial artery, elicited increases in skin and skeletal muscle vascular resistances which were always much less than those observed at corresponding brachial artery pressures during hemorrhage (Figures 9 and 11). These data agree with those in Series I, which indicated that hemorrhage-induced constriction in all skin and muscle vascular segments, including the large veins, results primarily from active smooth muscle contraction rather than from passive vascular collapse.

A comparison of the resistance data in Series I and II (Figures 10 and 12) reveals that the resistance response to hemorrhage in all forelimb vascular segments, except the large skin arteries, was not substantially attenuated by denervation. These data suggest that when the bleeding rate is rapid, and the blood loss severe enough to lower arterial blood pressure markedly (i.e., from a control value of 125

mm Hg to 100 mm Hg or below), blood-borne agents are the primary mediators of the vascular constriction in skin and skeletal muscle. Bond et al. (21) also observed that constriction of cutaneous vessels during large, rapid blood losses was not attenuated by denervation and therefore concluded that circulating hormones, rather than sympathetic nerves, are the primary mediators of hemorrhage-induced vasoconstriction in skin. In Bond et al.'s study, cutaneous vasoconstriction was also unaffected by bilateral nephrectomy, but was abolished by α adrenergic blockade, suggesting to them that circulating catecholamines mediated this response. In another study, Bond et al. (22) reported that circulating hormones and sympathetic nerves both mediate the vasoconstriction in skeletal muscle during rapid, severe hemorrhage. They observed that the resistance response to hemorrhage did not differ in innervated and denervated skeletal muscle vessels at perfusion pressures above 80 mm Hg. However, at perfusion pressures between 70 and 40 mm Hg, denervation reduced the resistance response to hemorrhage. Bond et al.'s data differ from those in the present study only at perfusion pressures of 70 mm Hg and below; our data indicate that denervation does not reduce hemorrhage-induced constriction in skeletal muscle vessels at pressures between 35 and 100 mm Hg. Differences between Bond et al.'s observations and those in the present study may be related to differences in the method of bleeding (5 ml/kg step hemorrhages

vs. 25 mm Hg step reductions in arterial pressure by rapid bleeding) or the preparation used (dog hindlimb muscle vs. dog forelimb muscle).

In the present study, the sympathetic nerves contributed significantly to the control of resting vascular resistance in skin and muscle, as evidenced by the reductions in resistance after denervation; but during rapid, severe hemorrhage, the nerves did not contribute appreciably to the increased vascular resistance, except in the large skin arteries.

III. Series III: Cross-perfused Forelimbs; Rapid, Arterial Hemorrhage of Recipient and Donor Dogs

This series of experiments was conducted to test the hypothesis that during rapid, severe hemorrhage, circulating vasoconstrictors and sympathetic nerves may be acting as simultaneous and overlapping mediators of skin and skeletal muscle vasoconstriction. That is, sympathetic nerves alone, or circulating vasoconstrictors alone, may cause forelimb resistance responses of similar magnitude to those observed when both factors act together. The results from Series I and II indicated that circulating vasoconstrictors can elicit increases in forelimb vascular resistance of similar magnitude to those observed when both neural and blood-borne factors are present; however, these studies did

not rule out the possibility that increased sympathetic nerve activity is also an important mediator of vasoconstriction in the forelimb during rapid, severe hemorrhage.

The cross-circulation technique used in the present study eliminated the hemorrhage-induced accumulation of vasoconstrictors in the arterial supply to the recipient dog's forelimb as long as the donor dog remained normotensive and normovolemic. The vasoconstriction which occurred in the forelimb when the recipient dog was bled can be attributed to a combination of the effects of increased sympathetic nerve activity and reduced forelimb perfusion pressure.

Bleeding the recipient dog elicited relatively small increases in forelimb vascular resistances (Figures 13 and 14). Total vascular resistance in skin and skeletal muscle increased only 4.2 and 3.4 fold respectively at the most severe level of hemorrhage. A significant part of these increased resistances was undoubtedly due to passive vascular collapse subsequent to reducing forelimb perfusion pressure, since the results of Series I and II indicate that reducing brachial artery pressure to 35 mm Hg alone results in a 1.2-2.5 fold increase in total skin or skeletal muscle vascular resistance. Therefore, when the recipient dog was hemorrhaged, increased sympathetic nerve activity elicited, at most, only a 3.0 and 2.2 fold increase in total skin and skeletal muscle vascular resistance respectively. These data

support the results of Series I and II which suggested that the contribution of sympathetic nerve activity to the increased forelimb vascular resistance during rapid, severe hemorrhage is modest relative to that due to circulating vasoconstrictors. The data in Series III do not support the hypothesis that circulating vasoconstrictors and sympathetic nerves are acting as simultaneous and overlapping mechanisms in eliciting skin and skeletal muscle vasoconstriction during rapid, severe hemorrhage.

After the shed blood was reinfused into the recipient dog and the forelimb nerves were severed, the forelimb vasculature was no longer reflexly controlled by the recipient dog. Therefore, vasoconstriction which accompanied hemorrhage of the donor dog can be attributed to passive vascular collapse due to reduced forelimb perfusion pressure, and to the effects of blood-borne vasoconstrictors released in the donor dog. Bleeding the donor dog to 35 mm Hg systemic arterial pressure elicited a 12.0 and 10.6 fold increase in total skin and skeletal muscle vascular resistance as compared to the 4.2 and 3.4 fold increase observed when the recipient dog was hemorrhaged to the same systemic arterial pressure. These data further support the hypothesis that circulating vasoconstrictors rather than sympathetic nerves, are the most important controllers of skin and skeletal muscle vessels during rapid, severe hemorrhage.

IV. Series IV: Naturally Perfused, Innervated or Denervated Forelimbs; Slow, Continuous Hemorrhage

A. Mean Systemic Arterial, Arterial Pulse, and Central Venous Pressures

A comparison of mean systemic arterial, arterial pulse, and central venous pressures between dogs with innervated and denervated forelimbs reveals that hemorrhage of 0.41 ml/kg body weight per minute produced the same pressure responses in both groups (Figure 15). These data indicate that both groups of dogs were subjected to similar bleeding stresses, a prerequisite for comparing resistance responses of innervated and denervated forelimbs.

B. Forelimb Resistances

In skin, slow, sustained hemorrhage (0.41 ml/kg body weight per minute) produced significant increases in total and all segmental vascular resistances of innervated and denervated forelimbs (Figure 16). In denervated forelimbs, the resistance increases were small; total skin resistance increased only 1.9 times above pre-hemorrhage control values. However, innervated forelimbs demonstrated a marked and progressive constriction in all skin vascular segments; total skin resistance increased more than 7.6 times above the control value. These data indicate that when the bleeding rate is slow, constriction of the skin vasculature is almost entirely neurogenically mediated.

Slow, sustained, hemorrhage produced significant increases in skeletal muscle total and segmental vascular resistances in innervated as well as denervated forelimbs, with the constriction being less pronounced in the denervated muscle vasculature (total resistance increased to 5.2 and 3.0 times above control in innervated and denervated forelimbs, respectively, after 60 minutes of bleeding) (Figure 17). These data demonstrate that denervation attenuates constriction of the muscle vasculature during slow hemorrhage. Since the denervated muscle vasculature still shows appreciable constriction during slow hemorrhage, circulating vasoconstrictors must mediate part of this response.

A comparison of the forelimb resistance responses to rapid and slow hemorrhage indicates that the relative importance of sympathetic nerves and blood-borne agents in mediating vasoconstriction depends on the rate of blood loss. When the bleeding rate is rapid, constriction in all forelimb vascular segments, except the large skin arteries, is not reduced by denervation. When the bleeding rate is much slower, denervation almost abolishes the hemorrhage-induced vasoconstriction in skin, and greatly attenuates it in skeletal muscle. These observations suggest that sympathetic nerves play a minor role in controlling vascular resistance during rapid, severe hemorrhage, but are much more important during slow, gradual blood losses.

These differences in the mediation of vasoconstriction do not appear to be related to differences in arterial baroreceptor stimulation during rapid and slow hemorrhage. For example, when mean arterial pressure was rapidly reduced to 75 mm Hg, increases in total skin and muscle vascular resistances were not significantly different in innervated and denervated forelimbs. In contrast, when mean arterial pressure is reduced to 75 mm Hg by slow hemorrhage, denervation almost abolishes the constriction in skin and greatly reduces it in muscle. Furthermore, several investigators (23,100,111) have reported that baroreceptor feedback is proportional not only to mean arterial pressure, but also to the derivative of the pressure. Therefore, rapid reduction of mean arterial pressure should produce a greater sympathetic nerve activity than should much slower reduction of mean arterial pressure to corresponding levels. These considerations suggest that differences in the relative importance of neurally mediated control of the skin and muscle vasculature during rapid and slow hemorrhage are not due to an arterial baroreceptor-mediated mechanism.

One explanation for the differences in vascular control during rapid and slow hemorrhage is that the release of circulating vasoconstrictors may depend on the rate of blood loss more than on the magnitude of the blood pressure reduction, with rapid hemorrhage eliciting a much greater release of circulating vasoconstrictors than slow hemorrhage even if

arterial blood pressure is equally reduced by both types of bleeding. This hypothesis is supported by Carey (28), who reported that slow, continuous hemorrhage (10% of the total blood volume in 30 min., or 30% in 90 min.) elicits no significant increase in adrenal epinephrine or norepinephrine secretion. Rapid hemorrhage (10% of the total blood volume in 10 min., or 30% in 30 min.) produced large increases in adrenal secretion of epinephrine and norepinephrine. Assuming that total blood volume in the dog is approximately 8 percent of body weight, the rate of blood loss in Series IV of the present study was about 15 percent of the total blood volume in 30 minutes (a rate somewhat higher than Carey's slow hemorrhage, but only one-half as great as his rapid hemorrhage rate). Therefore, the bleeding rate in Series IV may not have been great enough to elicit large increases in adrenal catecholamine secretion. In Series I and II, in which the bleeding rate was much more rapid, adrenal secretion of catecholamines would be expected to increase markedly and elicit a substantial constriction in the forelimb vasculature. It is also possible that the release of other circulating vasoconstrictors (i.e., angiotensin, vasopressin, and unidentified agents) is sensitive to the rate of blood loss.

SUMMARY AND CONCLUSIONS

1. A substantial reabsorption of extravascular fluid, which is not reduced by denervation, occurs in skin and skeletal muscle during rapid, severe hemorrhage.

2. The extravascular fluid reabsorption which accompanies hemorrhage results from a fall in capillary hydrostatic pressure, which in turn, results primarily from active changes in the pre- to postcapillary resistance ratio, and to a lesser extent, from a fall in arterial and venous pressures.

3. Hemorrhage-induced reductions in vascular capacitance are due primarily to active smooth muscle contraction rather than to passive vascular collapse subsequent to reduced transmural pressures. During rapid, severe hemorrhage, circulating vasoconstrictors mediate most of the active component of the decreased vascular capacitance.

4. Hemorrhage elicits a marked constriction in all skin and skeletal muscle vascular segments of the dog forelimb, whereas local hypotension produces relatively small increases in skin and skeletal muscle vascular resistances. These observations indicate that hemorrhage-induced constriction of all forelimb vascular segments, including the large veins, results largely from active smooth muscle contraction rather than from passive vascular collapse.

5. During rapid, severe hemorrhage, the increased resistance in all skin and muscle vascular segments, except the large skin arteries, is not substantially reduced by denervation. When hemorrhage-induced circulating vasoconstrictors are prevented from accumulating in the forelimb by using a cross-circulation technique, increases in skin and skeletal muscle vascular resistances during rapid, severe hemorrhage are modest. These observations suggest that circulating vasoconstrictors, rather than sympathetic nerves, are the primary mediators of active constriction in the skin and muscle vasculature during rapid, severe hemorrhage.

6. During slow, sustained hemorrhage (0.41 ml blood loss/kg body weight per minute) denervation almost abolishes the constrictor response in the skin vasculature and greatly attenuates it in skeletal muscle, indicating that sympathetic nerves are much more important in mediating vasoconstriction during slow hemorrhage than during rapid, severe hemorrhage. However, circulating vasoconstrictors mediate part of the forelimb resistance response to slow hemorrhage as evidenced by the constriction which occurred in skeletal muscle even after denervation.

APPENDICES

APPENDIX A

LIST OF ABBREVIATIONS AND FORELIMB VASCULAR RESISTANCE CALCULATIONS

APPENDIX A

LIST OF ABBREVIATIONS AND FORELIMB VASCULAR RESISTANCE CALCULATIONS

1. Vascular Resistances = R in mm Hg x $(ml/min)^{-1}$

   ST = skin total

   SA = skin large artery

   SSV = skin small vessel

   SV = skin large vein

   MT = muscle total

   MA = muscle large artery

   MSV = muscle small vessel

   MV = muscle large vein

2. Pressures = P in mm Hg

   SYS = mean systemic arterial

   BA = brachial artery

   CV = cephalic vein

   SSA = skin small artery

   SSVE = skin small vein

   BV = brachial vein

   MSA = muscle small artery

   MSVE = muscle small vein

3. Blood Flows = F in ml/min

   C = cephalic

   B = brachial

4. Forelimb Vascular Resistance Calculations

$$R_{ST} = (P_{BA} - P_{CV}) / F_C$$

$$R_{SA} = (P_{BA} - P_{SSA}) / F_C$$

$$R_{SSV} = (P_{SSA} - P_{SSVE}) / F_C$$

$$R_{SV} = (P_{SSVE} - P_{CV}) / F_C$$

$$R_{MT} = (P_{BA} - P_{BV}) / F_B$$

$$R_{MA} = (P_{BA} - P_{MSA}) / F_B$$

$$R_{MSV} = (P_{MSA} - P_{MSVE}) / F_B$$

$$R_{MV} = (P_{MSVE} - P_{BV}) / F_B$$

APPENDIX B

PRESSURE, FLOW, AND RESISTANCE DATA

Table B-1. Effects of local hypotension and rapid arterial hemorrhage on systemic arterial pressure and arterial pressures in innervated forelimbs. Values in mm Hg are means ± standard errors from 16 experiments.

	P_{BA}	P_{SYS}	P_{SSA}	P_{MSA}
Control	122.3±2.8	128.9±2.8	99.5±3.1	103.6±2.9
Clamp	100.0±0.5	134.9±2.2	82.5±1.5	86.4±1.1
	76.1±0.6	130.7±2.8	62.4±0.9	64.5±0.9
	51.9±0.5	131.3±2.6	42.0±0.6	43.1±0.8
	34.8±0.6	133.6±2.7	27.5±0.6	27.9±0.6
Control	123.3±2.9	130.9±2.8	97.7±3.3	105.4±2.9
Bleed	98.9±0.6	104.5±1.2	83.2±1.2	88.6±0.9
	74.2±0.6	79.7±0.8	60.4±1.2	65.4±0.7
	50.5±0.7	54.4±0.8	40.7±0.9	42.3±0.7
	35.9±0.5	38.6±0.8	28.9±0.7	28.6±0.8

Table B-2. Effects of local hypotension and rapid arterial hemorrhage on venous pressures (mm Hg) and blood flows (ml/min) in innervated forelimbs. Values are means ± standard errors from 16 experiments.

	P_{SSVE}	P_{CV}	P_{MSVE}	P_{BV}	F_C	F_B
Control	12.6±0.5	7.2±0.6	7.4±0.3	4.5±0.3	71.1±6.3	47.8±2.9
Clamp	10.7±1.1	5.1±0.5	5.6±0.4	2.9±0.3	59.0±7.0	33.2±2.7
	7.6±0.4	3.4±0.4	4.7±0.3	2.1±0.3	43.5±3.4	21.0±1.3
	6.8±0.5	1.6±0.4	3.7±0.3	1.4±0.2	28.0±2.1	11.2±0.7
	4.6±0.5	0.8±0.4	3.0±0.3	1.1±0.2	16.8±1.3	6.3±0.4
Control	13.6±0.6	7.3±0.7	8.0±0.4	4.6±0.3	68.8±5.3	46.9±3.2
Bleed	8.1±0.5	2.7±0.4	4.9±0.4	2.0±0.2	36.0±6.5	16.9±2.3
	5.9±0.4	1.2±0.4	4.4±0.4	1.5±0.2	24.5±3.2	7.2±0.9
	4.4±0.5	0.1±0.4	4.0±0.4	1.2±0.2	10.7±1.7	2.8±0.3
	4.3±0.4	-0.3±0.4	3.7±0.4	1.0±0.2	5.6±0.9	1.8±0.2

Table B-3. Effects of local hypotension and rapid arterial hemorrhage on the percent of total skin or skeletal muscle resistance residing in innervated large arteries, small vessels, and large veins. P_{BA} = brachial artery pressure in mm Hg. Values are means from 16 experiments.

		SKIN			SKELETAL MUSCLE		
	P_{BA}	Large Arteries	Small Vessels	Large Veins	Large Arteries	Small Vessels	Large Veins
Control	122.3	16.2	79.2	4.6	16.6	79.9	3.5
Clamp	100.0	14.9	80.0	5.1	14.7	81.6	3.7
	76.1	16.5	77.4	6.1	17.2	78.7	6.1
	51.9	18.4	72.6	9.0	19.3	76.0	4.8
	34.8	21.2	66.7	12.1	22.9	70.8	6.4
Control	123.3	19.1	75.5	5.4	16.4	80.1	3.5
Bleed	98.9	12.6	82.6	4.8	12.7	83.9	3.5
	74.2	14.5	78.4	7.1	14.5	81.0	4.5
	50.5	16.2	74.9	8.9	21.2	72.4	6.4
	35.9	15.7	69.5	14.9	25.7	65.4	8.9

Table B-4. Effects of denervation, local hypotension, and rapid arterial hemorrhage on systemic arterial and forelimb arterial pressures. Values in mm Hg are means ± standard errors from 17 experiments.

	P_{BA}	P_{SYS}	P_{SSA}	P_{MSA}
		BEFORE DENERVATION		
Control	122.7±1.7	129.7±1.8	95.3±2.1	105.8±2.0
		AFTER DENERVATION		
Control	114.7±2.1	125.8±2.1	70.5±2.0	95.0±2.2
Clamp	99.3±0.5	135.6±2.0	61.1±2.3	79.6±1.5
	76.4±0.4	128.0±2.5	49.5±1.3	63.0±1.0
	51.0±0.4	129.5±2.4	32.5±0.7	39.4±1.0
	34.4±0.4	130.2±2.3	21.2±0.6	24.7±0.8
Control	116.6±1.9	129.7±2.0	69.1±1.9	93.7±2.3
Bleed	100.0±0.9	108.8±0.9	68.6±2.7	82.5±2.0
	76.7±0.3	85.3±0.8	58.6±1.6	64.7±1.1
	52.9±0.3	57.5±0.6	43.3±1.3	43.7±0.8
	35.7±0.3	39.2±0.5	31.1±1.6	28.2±0.7

Table B-5. Effects of denervation, local hypotension, and rapid arterial hemorrhage on forelimb venous pressures (mm Hg) and blood flows (ml/min). Values are means ± standard errors from 17 experiments.

	P_{SSVE}	P_{CV}	P_{MSVE}	P_{BV}	F_C	F_B
			BEFORE DENERVATION			
Control	13.4±0.6	6.3±0.5	8.8±0.5	4.9±0.3	91.4±3.7	57.4±3.2
			AFTER DENERVATION			
Control	19.6±0.7	10.2±0.7	11.3±0.5	6.4±0.4	120.2±5.2	79.2±4.6
Clamp	14.8±0.5	7.5±0.6	9.4±0.5	5.4±0.5	98.4±4.5	55.8±4.2
	11.3±0.3	5.2±0.4	6.9±0.3	3.6±0.3	81.6±2.8	41.7±2.7
	7.3±0.3	2.2±0.3	5.2±0.4	2.0±0.3	54.8±2.2	20.5±1.0
	5.4±0.2	0.3±0.2	4.2±0.3	1.2±0.3	32.8±1.3	10.2±0.6
Control	21.8±1.0	11.8±0.9	12.8±0.7	7.9±0.6	126.8±4.2	82.6±4.9
Bleed	12.0±0.7	5.4±0.7	7.3±0.6	4.6±0.6	70.2±4.7	29.2±3.4
	8.2±0.5	1.6±0.4	4.9±0.3	2.2±0.3	45.6±4.5	19.9±3.3
	5.5±0.4	-0.8±0.3	4.7±0.3	1.1±0.3	12.3±1.8	6.2±1.4
	4.4±0.4	-1.8±0.2	4.7±0.5	0.7±0.3	3.3±0.4	2.7±0.5

Table B-6. Effects of denervation, local hypotension, and rapid arterial hemorrhage on the percent of total skin or skeletal muscle vascular resistance residing in large arteries, small vessels, and large veins. P_{BA} = brachial artery pressure in mm Hg. Values are means from 17 experiments.

	P_{BA}	SKIN			SKELETAL MUSCLE		
		Large Arteries	Small Vessels	Large Veins	Large Arteries	Small Vessels	Large Veins
				BEFORE DENERVATION			
Control	122.7	22.1	71.6	6.3	14.9	81.8	3.3
				AFTER DENERVATION			
Control	114.7	41.0	50.0	9.0	17.9	77.8	4.2
Clamp	99.3	40.1	51.5	8.2	19.3	77.0	3.7
	76.4	37.2	54.3	8.5	17.7	78.2	4.1
	51.0	37.6	51.9	10.5	23.6	71.0	5.6
	34.4	39.6	45.3	15.0	30.5	62.2	7.3
Control	116.6	44.8	46.0	9.2	20.9	74.7	4.4
Bleed	100.0	25.1	68.1	6.8	8.4	89.4	2.2
	76.7	9.7	82.6	7.6	13.2	84.1	2.7
	52.9	8.3	79.3	12.4	16.8	77.8	5.4
	35.7	8.7	73.7	17.6	22.0	68.7	9.3

Table B-7. Effects of rapid arterial hemorrhage on systemic arterial pressure in donor (P_{SYSD}) and recipient (P_{SYSR}) dogs and on arterial pressures in cross-perfused forelimbs. Values in mm Hg are means ± standard errors from 5 experiments.

	P_{SYSD}	P_{SYSR}	P_{BA}	P_{SSA}	P_{MSA}
Control	116.1±2.2	129.4+2.9	106.3±2.8	68.8±4.4	82.8±3.7
Bleed Recipient	115.4±2.9	98.3±1.9	100.0±0.0	60.9±3.3	78.7±3.1
	113.9±2.8	77.1±1.0	75.0±0.0	43.8±1.9	56.8±2.2
	114.6±2.5	50.7±0.7	50.0±0.0	24.3±7.2	37.7±1.6
	114.3±2.7	36.7±1.4	35.4±0.2	15.1±4.7	24.7±1.0
Control	117.7±2.4	125.9±2.2	104.7±2.5	61.9±3.4	83.2±3.0
Bleed Donor	96.7±2.0	121.3±6.6	100.0±0.0	57.7±4.2	85.0±3.3
	74.1±1.4	121.9±3.7	74.8±0.2	50.6±1.4	62.6±0.7
	54.1±0.9	119.6±3.3	49.1±0.5	27.8±4.4	38.2±0.7
	37.0±0.9	115.0±3.8	34.2±0.4	19.0±1.8	28.9±0.9

Table B-8. Effects of rapid arterial hemorrhage on venous pressures (mm Hg) and blood flows (ml/min) in cross-perfused forelimbs. Values are means ± standard errors from 5 experiments.

	P_{SSVE}	P_{CV}	P_{MSVE}	P_{BV}	F_C	F_B
Control	16.4±1.0	9.1±1.0	8.6±0.6	4.2±0.7	133.2±5.4	73.6±3.6
Bleed Recipient	15.7±1.0	8.5±1.2	7.4±0.9	4.0±0.9	125.2±8.0	66.4±4.3
	9.8±0.4	4.7±0.6	5.5±0.8	2.1±0.7	77.7±5.5	34.9±2.1
	5.7±0.2	1.9±0.3	3.9±0.7	0.7±0.5	28.2±2.5	14.6±1.1
	4.9±0.2	1.1±0.2	3.0±0.5	-0.2±0.2	11.8±0.9	7.7±0.6
Control	18.2±1.3	10.5±1.5	10.3±1.1	3.9±0.7	130.4±3.7	77.0±5.8
Bleed Donor	19.7±0.2	12.5±1.1	10.0±0.4	3.3±0.5	102.1±4.8	68.4±5.8
	9.5±0.9	4.6±0.9	3.9±0.5	-0.1±0.2	50.4±5.6	19.3±2.9
	7.3±0.8	2.2±0.4	2.4±0.2	-1.2±0.4	14.8±2.3	5.8±0.7
	7.2±0.5	1.4±0.5	2.2±0.4	-1.8±0.4	5.4±0.7	2.6±0.2

Table B-9. Effects of rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) of skin arteries (SA), small vessels (SSV), and veins (SV) in cross-perfused forelimbs. P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 5 experiments.

	P_{BA}	$\bar{P}_{SA}$	$\bar{P}_{SSV}$	$\bar{P}_{SV}$
Control	106.3±2.8	87.5±3.5	42.6±2.0	12.7±1.0
Bleed Recipient	100.0±0.0	80.5±1.7	38.3±1.3	12.1±1.0
	75.0±0.0	59.4±1.0	26.8±0.8	7.3±0.5
	50.0±0.0	37.2±0.9	15.0±0.9	3.8±0.2
	35.4±0.2	25.3±0.7	10.0±0.6	3.0±0.1
Control	104.7±2.5	83.3±2.8	40.1±1.6	14.4±1.4
Bleed Donor	100.0±0.0	78.8±2.1	38.7±2.2	12.1±0.6
	74.8±0.2	62.7±0.7	30.1±0.7	7.0±0.9
	49.1±0.5	42.8±0.6	21.8±0.9	4.8±0.6
	34.2±0.4	30.5±0.4	17.0±0.5	4.3±0.5

Table B-10. Effects of rapid arterial hemorrhage on mean intraluminal pressure ($\bar{P}$) of muscle arteries (MA), small vessels (MSV), and veins (MV) in cross-perfused forelimbs. P_{BA} = brachial artery pressure. Values in mm Hg are means ± standard errors from 5 experiments.

	P_{BA}	$\bar{P}_{MA}$	$\bar{P}_{MSV}$	$\bar{P}_{MV}$
Control	106.3±2.8	94.5±3.1	45.2±2.2	5.8±0.5
Bleed Recipient	100.0±0.0	89.3±1.6	41.5±1.4	5.0±0.8
	75.0±0.0	65.9±1.1	30.0±0.8	3.2±0.5
	50.0±0.0	43.9±0.8	20.4±0.6	1.9±0.4
	35.4±0.2	30.1±0.6	13.6±0.4	1.2±0.3
Control	104.7±2.5	94.0±2.6	46.7±1.4	7.0±0.9
Bleed Donor	100.0±0.0	92.5±0.7	47.5±0.9	6.7±0.5
	74.8±0.2	68.7±0.4	33.2±0.5	1.9±0.3
	49.1±0.5	43.7±0.5	20.3±0.4	0.6±0.2
	34.2±0.4	31.5±0.6	15.5±0.5	0.2±0.2

Table B-11. Effects of rapid arterial hemorrhage on the percent of total skin or skeletal muscle resistance residing in large arteries, small vessels, and large veins in cross-perfused forelimbs. P_{BA} = brachial artery pressure in mm Hg. Values are means from 5 experiments.

	P_{BA}	SKIN			SKELETAL MUSCLE		
		Large Arteries	Small Vessels	Large Veins	Large Arteries	Small Vessels	Large Veins
Control	106.3	37.8	55.4	6.8	21.7	73.0	5.3
Bleed Recipient	100.0	40.2	51.9	7.9	20.4	74.5	5.1
	75.0	42.4	50.5	7.1	23.2	70.4	6.3
	50.0	54.4	38.1	7.5	23.3	69.3	7.4
	35.4	58.9	30.4	10.7	29.4	61.7	8.9
Control	104.7	44.6	47.3	8.1	20.9	73.4	5.7
Bleed Donor	100.0	47.1	44.8	8.1	16.3	76.9	6.8
	74.8	29.9	64.0	6.1	16.9	79.0	4.1
	49.1	22.6	66.7	10.7	22.2	71.0	6.8
	34.2	20.0	63.1	16.9	14.8	74.0	11.2

Table B-12. Effects of slow, continuous hemorrhage on systemic arterial pressure and arterial pressures in innervated forelimbs. Values in mm Hg are means ± standard errors from 8 experiments. MIN = time in minutes after the onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight.

MIN	P_{BA}	P_{SYS}	P_{SSA}	P_{MSA}	Blood Loss
0	110.3±1.9	114.7±2.0	89.3±2.0	95.5±1.8	0.00
2	109.1±3.1	113.4±3.1	88.0±3.5	93.6±3.1	0.81
4	108.4±3.2	112.6±3.2	87.9±3.8	93.9±3.2	1.63
6	107.2±4.1	112.0±3.7	87.4±3.7	91.9±3.1	2.44
8	105.6±4.4	110.1±4.0	86.6±4.0	91.9±3.0	3.20
10	105.4±4.6	110.1±4.4	86.6±4.4	91.9±3.4	4.07
12	103.6±5.5	108.9±4.3	86.1±4.7	90.7±4.2	4.88
14	102.2±6.0	106.6±5.8	84.9±5.7	90.4±4.8	5.70
16	101.1±6.2	105.2±6.2	82.9±5.7	88.0±5.1	6.51
18	97.8±6.9	104.0±6.7	82.0±6.2	87.1±5.7	7.33
20	98.5±7.3	102.9±7.3	81.4±6.6	86.7±6.2	8.14
22	97.6±7.8	101.9±7.5	80.9±7.0	85.6±6.3	8.95
24	96.4±7.7	100.7±7.5	79.6±6.8	84.0±6.2	9.77
26	94.5±7.7	98.8±7.4	78.6±6.9	82.9±6.4	10.58
28	92.9±7.8	97.1±7.5	77.5±7.2	81.9±6.6	11.40
30	91.3±7.7	95.4±7.5	76.0±6.9	81.0±6.5	12.21
32	89.9±7.7	94.0±7.7	74.0±6.8	78.9±6.4	13.02
34	87.7±7.7	91.6±7.8	73.4±7.0	76.7±6.7	13.84
36	85.1±7.5	89.5±7.4	72.4±7.1	76.4±6.9	14.65
38	83.8±7.7	88.0±7.5	70.5±7.1	73.8±6.8	15.47
40	81.4±7.6	85.0±7.5	70.0±7.1	73.0±6.7	16.28
42	80.0±7.4	83.9±7.3	69.4±7.0	71.5±7.0	17.09
44	78.2±7.1	82.0±7.1	66.4±6.8	69.4±6.5	17.91
46	76.7±6.9	81.0±6.8	65.1±6.8	67.5±6.6	18.72
48	75.0±6.9	79.1±6.7	64.2±6.8	67.1±6.5	19.54
50	73.0±6.5	77.0±6.5	62.1±6.7	65.1±6.4	20.35
52	70.4±6.2	74.2±6.2	61.1±6.3	63.4±6.2	21.16
54	68.1±6.5	72.0±6.5	58.0±6.9	59.6±6.7	21.98
56	65.6±6.4	69.4±6.6	56.5±6.8	57.5±6.7	22.79
58	62.4±6.2	65.7±6.4	53.6±6.6	54.7±6.8	23.61
60	60.0±6.5	63.5±6.5	51.7±6.3	52.4±6.7	24.42

Table B-13. Effects of slow, continuous hemorrhage on venous pressures (mm Hg) and blood flows (ml/min) in innervated forelimbs. Values are means ± standard errors from 8 experiments. MIN = time in minutes after the onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight.

MIN	P_{SSVE}	P_{CV}	P_{MSVE}	P_{BV}	F_C	F_B	Blood Loss
0	13.2±0.7	7.3±0.7	9.9±0.6	4.7±0.4	94.6± 6.8	56.4±4.3	0.00
2	13.1±1.3	7.1±1.4	9.5±1.2	4.4±0.7	90.1±12.4	52.1±7.3	0.82
4	12.9±1.3	6.8±1.4	9.4±1.1	4.3±0.7	88.8±12.5	51.5±7.0	1.63
6	12.6±1.3	6.5±1.3	9.2±1.1	4.1±0.7	86.3±12.8	49.2±6.6	2.44
8	12.4±1.3	6.3±1.3	9.0±101	3.9±0.7	83.2±13.1	47.6±7.2	3.20
10	12.1±1.3	6.3±1.3	8.9±1.2	3.8±0.7	79.4±12.9	44.3±6.6	4.07
12	11.8±1.3	6.0±1.3	8.6±1.1	3.7±0.7	76.2±12.9	41.9±6.1	4.88
14	11.6±1.2	5.8±1.3	8.4±1.2	3.5±0.7	73.4±12.7	40.4±6.2	5.70
16	11.5±1.2	5.4±1.3	8.2±1.2	3.3±0.7	70.2±13.2	38.1±6.7	6.51
18	11.4±1.3	5.3±1.3	8.1±1.3	3.2±0.7	67.3±13.2	36.1±6.3	7.33
20	11.1±1.3	5.3±1.2	7.8±1.2	3.2±0.7	64.4±12.8	35.3±6.4	8.14
22	11.0±1.2	5.2±1.3	7.5±1.2	3.0±0.8	63.3±12.8	33.4±6.2	8.95
24	10.9±1.2	4.9±1.3	7.3±1.1	2.8±0.7	61.4±12.6	31.7±5.8	9.77
26	10.7±1.2	4.8±1.3	7.3±1.2	2.7±0.7	58.7±12.8	29.2±4.6	10.58
28	10.5±1.2	4.6±1.3	7.1±1.1	2.7±0.7	55.5±13.2	26.0±3.8	11.40
30	10.1±1.1	4.5±1.3	7.0±1.2	2.5±0.7	51.3±12.2	26.0±4.9	12.21
32	9.9±1.2	4.3±1.3	6.8±1.2	2.4±0.7	50.4±12.8	25.2±5.2	13.02
34	9.9±1.2	4.1±1.3	6.9±1.3	2.3±0.7	45.4±12.7	23.5±4.8	13.84
36	9.6±1.2	3.9±1.3	6.6±1.2	2.2±0.7	42.4±12.1	20.8±3.8	14.65
38	9.1±1.0	3.6±1.2	6.3±1.1	2.0±0.7	40.0±12.0	19.1±3.3	15.47
40	8.9±1.0	3.5±1.1	6.2±1.1	1.9±0.7	35.2±10.8	17.2±3.1	16.28
42	8.9±1.0	3.2±1.1	6.1±1.1	1.7±0.7	33.5±10.6	15.5±2.8	17.09
44	8.7±1.0	3.1±1.0	5.8±1.1	1.7±0.7	30.7±10.4	14.2±2.3	17.91
46	8.4±0.9	2.8±1.0	5.8±1.0	1.5±0.6	28.8± 9.4	13.1±2.0	18.72
48	8.2±0.8	2.7±0.9	5.7±1.0	1.4±0.6	27.6± 9.5	12.5±2.0	19.54
50	8.0±0.8	2.3±0.9	5.6±1.0	1.3±0.6	24.1± 8.7	10.9±1.6	20.35
52	7.9±0.8	2.1±0.8	5.4±1.0	1.3±0.6	21.2± 7.9	9.7±1.3	21.16
54	7.5±0.8	1.9±0.7	5.4±1.0	1.2±0.6	18.5± 7.3	8.7±1.2	21.98
56	7.3±0.8	1.5±0.6	5.2±1.0	1.1±0.6	15.9± 5.9	7.9±1.1	22.79
58	7.0±0.8	1.2±0.6	5.2±1.0	1.0±0.6	13.8± 4.7	7.2±1.1	23.61
60	6.8±0.7	1.1±0.5	5.1±1.0	1.0±0.5	12.3± 4.3	6.6±1.0	24.42

Table B-14. Effects of slow, continuous hemorrhage on systemic arterial pressure and arterial pressures in denervated forelimbs. Values in mm Hg are means ± standard errors from 9 experiments. MIN = time in minutes after the onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight.

MIN	P_{BA}	P_{SYS}	P_{SSA}	P_{MSA}	Blood Loss
0	104.6±1.9	115.2±2.8	61.7±1.3	85.9±1.2	0.00
2	103.9±3.7	114.6±5.4	61.2±2.4	86.0±2.6	1.81
4	103.0±3.6	114.3±5.5	61.1±2.3	85.9±2.9	1.63
6	102.6±3.6	113.2±5.2	61.0±2.2	85.0±2.9	2.44
8	102.1±3.6	112.6±5.4	60.8±2.2	85.3±2.9	3.27
10	101.6±3.5	111.9±5.4	60.4±2.4	84.9±2.8	4.07
12	100.9±3.7	111.4±5.4	59.8±2.3	84.6±3.1	4.88
14	101.0±3.8	110.9±5.2	59.9±2.3	84.8±3.3	5.70
16	100.1±3.8	110.3±5.2	60.1±2.4	84.7±3.3	6.51
18	98.8±3.8	109.4±5.3	58.9±2.4	83.9±3.3	7.33
20	97.8±3.8	107.6±4.9	58.0±2.6	83.6±3.4	8.14
22	97.1±3.9	106.7±5.1	58.1±2.6	82.7±3.4	8.95
24	97.0±3.9	106.6±5.1	57.1±2.8	81.9±3.2	9.77
26	95.0±4.0	104.9±5.0	55.8±2.9	80.7±3.3	10.58
28	92.8±3.9	102.8±4.9	55.4±3.0	79.1±3.7	11.40
30	90.6±4.2	100.6±5.1	53.3±3.2	78.1±3.6	12.21
32	89.7±4.0	99.1±4.8	53.9±3.0	77.3±3.5	13.02
34	88.3±4.0	97.9±4.7	53.4±3.1	75.3±4.1	13.84
36	85.8±4.6	95.0±5.2	52.8±3.2	73.7±4.2	15.47
38	83.9±4.7	92.7±5.1	51.4±3.3	71.8±4.2	15.47
40	82.8±4.9	91.7±5.4	51.0±3.4	70.7±4.2	16.28
42	81.2±4.9	89.4±5.0	50.4±3.4	69.4±4.5	17.09
44	80.2±4.8	88.6±4.9	50.0±3.3	69.2±4.2	17.91
46	79.4±4.5	87.9±4.6	49.8±2.8	67.1±4.5	18.72
48	76.2±4.9	85.0±4.7	48.9±3.0	64.9±4.5	19.54
50	74.8±5.3	82.7±5.2	48.8±3.1	63.4±4.6	20.35
52	72.9±5.4	80.8±5.2	46.7±3.8	61.6±4.7	21.16
54	71.8±5.5	79.8±5.4	46.1±4.1	59.6±5.1	21.98
56	69.0±5.3	77.3±5.4	45.3±4.1	58.7±4.7	22.79
58	67.9±5.1	76.2±5.1	44.6±3.8	56.7±4.7	23.61
60	65.4±5.3	73.4±5.6	42.9±3.7	54.7±4.7	24.42

Table B-15. Effects of slow, continuous hemorrhage on venous pressures (mm Hg) and blood flows (ml/min) in denervated forelimbs. Values are means ± standard errors from 9 experiments. MIN = time in minutes after the onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight.

MIN	P_{SSVE}	P_{CV}	P_{MSVE}	P_{BV}	F_C	F_B	Blood Loss
0	19.5±0.6	12.1±0.6	10.8±0.5	6.7±0.5	126.9± 8.7	65.1± 5.0	0.00
2	19.4±1.1	11.9±1.1	10.8±0.9	6.7±0.9	126.2±16.5	64.4±10.8	1.81
4	19.1±1.1	11.7±1.1	10.8±1.0	6.6±0.9	124.6±16.0	63.3± 9.4	1.63
6	18.6±1.1	11.5±1.1	10.5±1.0	6.6±0.9	121.2±15.1	60.8± 9.0	2.44
8	18.5±1.1	11.3±1.1	10.3±1.0	6.4±0.9	118.3±14.5	58.9± 8.5	3.27
10	18.4±1.2	11.2±1.1	10.1±1.0	6.4±0.8	117.9±14.7	57.9± 9.0	4.07
12	18.1±1.2	11.2±1.1	10.2±1.0	6.3±0.9	115.9±14.3	56.3± 9.1	4.88
14	18.1±1.2	11.0±1.1	10.1±0.9	6.2±0.8	115.6±14.4	54.4± 9.2	5.70
16	17.6±1.2	10.8±1.1	9.7±0.9	6.1±0.8	111.7±13.2	52.6± 8.4	6.51
18	17.4±1.1	10.4±1.1	9.5±0.8	5.8±0.6	109.0±12.7	51.3± 8.0	7.33
20	17.0±1.1	10.2±1.1	9.3±0.8	5.6±0.6	105.8±12.3	49.5± 8.0	8.14
22	16.7±1.0	10.1±1.1	9.0±0.7	5.5±0.6	105.2±12.8	48.2± 8.7	8.95
24	16.6±1.1	10.0±1.1	9.0±0.7	5.5±0.7	102.7±12.5	46.7± 8.2	9.77
26	16.3±1.1	9.7±1.1	8.8±0.7	5.4±0.7	100.4±12.5	44.9± 8.2	10.58
28	15.8±1.0	9.4±1.1	8.3±0.8	5.2±0.7	96.8±11.8	42.0± 8.1	11.40
30	15.0±1.1	9.1±1.2	8.1±0.7	5.0±0.7	93.9±12.6	40.0± 8.4	12.21
32	14.7±1.0	8.9±1.1	8.0±0.7	4.9±0.7	91.3±12.1	39.4± 8.3	13.02
34	14.5±1.0	8.8±1.1	8.0±0.7	4.7±0.8	89.1±12.1	38.4± 8.3	13.84
36	14.1±1.1	8.5±1.2	7.8±0.7	4.6±0.8	84.5±12.4	35.5± 8.4	14.65
38	13.5±1.1	8.2±1.1	7.6±0.7	4.4±0.9	81.9±13.0	33.8± 8.4	15.47
40	13.7±1.1	8.0±1.2	7.5±0.7	4.3±0.9	78.8±12.8	32.0± 8.0	16.28
42	12.8±1.1	7.7±1.2	7.3±0.7	4.1±0.8	75.0±12.5	31.4± 8.3	17.09
44	12.6±1.1	7.6±1.2	7.3±0.7	4.1±0.8	72.8±12.3	29.5± 8.4	17.91
46	12.3±1.0	7.1±0.9	7.1±0.7	4.0±0.8	70.3±12.0	28.4± 7.9	18.72
48	11.8±0.9	6.8±0.9	6.9±0.7	3.9±0.8	67.5±12.3	27.2± 8.1	19.54
50	11.4±0.8	6.4±0.8	6.7±0.7	3.6±0.8	64.0±11.9	25.7± 7.7	20.35
52	11.2±0.8	6.3±0.8	6.4±0.6	3.6±0.8	61.8±12.1	24.6± 7.8	21.16
54	10.8±0.8	6.0±0.7	6.5±0.6	3.5±0.8	59.2±11.7	23.8± 7.6	21.98
56	10.5±0.8	5.7±0.7	6.5±0.6	3.4±0.7	56.0±11.0	22.0± 6.9	22.79
58	10.1±0.7	5.4±0.7	6.4±0.6	3.2±0.7	52.1±10.1	20.1± 6.0	23.61
60	9.8±0.6	5.1±0.7	6.1±0.6	3.0±0.6	48.6±10.2	19.1± 6.1	24.42

Table B-16. Effects of slow, continuous hemorrhage on the percent of total skin or skeletal muscle resistance residing in innervated large arteries, small vessels, and large veins. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means from 8 experiments.

	SKIN			SKELETAL MUSCLE			
MIN	Large Arteries	Small Vessels	Large Veins	Large Arteries	Small Vessels	Large Veins	Blood Loss
0	17.8	76.3	6.0	13.8	81.0	5.1	0.00
2	17.9	76.4	5.7	13.6	81.4	5.0	0.81
4	18.5	75.6	5.9	14.8	80.4	4.8	1.63
6	17.7	76.3	6.0	14.0	81.0	5.0	2.44
8	17.0	77,0	6.0	14.7	80.3	5.0	3.20
10	16.5	77.3	6.2	13.0	81.9	5.1	4.07
12	16.4	77.7	6.0	13.0	82.1	5.0	4.88
14	15.0	78.9	6.1	12.7	82.3	5.0	5.70
16	15.6	78.0	6.3	11.7	83.1	5.1	6.51
18	16.8	76.6	6.6	13.4	81.5	5.1	7.33
20	16.2	77.0	6.8	13.0	81.8	5.2	8.14
22	16.4	76.8	6.8	12.1	82.8	5.1	8.95
24	15.8	77.7	6.8	11.9	83.1	5.0	9.77
26	15.4	77.5	7.1	12.7	82.3	5.0	10.58
28	15.3	77.4	7.3	12.5	82.4	5.1	11.40
30	14.9	77.5	7.6	12.3	82.8	4.9	12.21
32	14.6	77.9	7.5	10.9	84.1	5.0	13.02
34	16.0	76.7	7.3	12.9	82.2	4.9	13.84
36	14.1	78.1	7.7	13.2	81.6	5.2	14.65
38	12.5	79.6	7.9	11.1	83.8	5.1	15.47
40	12.9	79.2	7.8	12.3	82.5	5.1	16.28
42	9.7	82.2	8.0	10.7	84.1	5.3	17.09
44	8.0	83.8	8.2	11.9	82.7	5.4	17.91
46	10.0	81.9	8.0	11.5	83.2	5.3	18.72
48	10.5	81.4	8.1	12.6	81.8	5.5	19.54
50	9.3	82.5	8.2	11.3	83.1	5.6	20.35
52	10.2	81.4	8.4	11.5	82.8	5.7	21.16
54	8.6	82.5	8.9	12.3	81.9	5.8	21.98
56	10.8	80.4	8.9	14.3	79.5	6.2	22.79
58	10.2	80.6	9.2	14.6	79.1	6.2	23.61
60	10.2	80.6	9.2	14.7	78.8	6.5	24.42

Table B-17. Effects of slow, continuous hemorrhage on the percent of total skin or skeletal muscle resistance residing in denervated large arteries, small vessels, and large veins. MIN = time in minutes after onset of bleeding. Blood Loss = accumulated blood loss in ml/kg body weight. Values are means from 9 experiments.

	SKIN			SKELETAL MUSCLE			
MIN	Large Arteries	Small Vessels	Large Veins	Large Arteries	Small Vessels	Large Veins	Blood Loss
0	44.4	47.9	7.7	18.8	76.8	4.4	0.00
2	44.9	47.3	7.9	18.2	77.5	4.4	0.81
4	44.7	47.5	7.8	17.8	77.8	4.5	1.63
6	44.2	47.9	7.9	18.2	77.4	4.3	2.44
8	44.1	48.2	7.8	17.8	78.1	4.1	3.20
10	44.4	48.0	7.7	17.7	78.3	4.0	4.07
12	44.4	48.0	7.6	17.4	78.5	4.1	4.88
14	44.4	47.9	7.6	17.4	78.4	4.2	5.70
16	43.7	48.8	7.5	17.0	79.0	3.9	6.51
18	44.1	48.1	7.8	16.6	79.4	3.9	7.33
20	44.5	47.8	7.7	16.1	79.9	3.9	8.14
22	43.9	48.5	7.6	16.2	80.0	3.8	8.95
24	44.8	47.7	7.5	17.0	79.2	3.8	9.77
26	44.9	47.4	7.7	16.5	79.7	3.8	10.58
28	44.1	48.3	7.7	16.5	79.7	3.8	11.40
30	43.5	49.2	7.3	15.5	80.7	3.9	12.21
32	43.2	49.6	7.2	15.1	80.9	4.0	13.02
34	42.8	49.9	7.2	16.5	79.2	4.2	13.89
36	41.5	51.3	7.2	15.7	79.9	4.4	14.65
38	41.2	51.9	6.9	16.2	79.3	4.5	15.47
40	41.1	51.9	7.0	16.1	79.2	4.7	16.28
42	40.4	52.9	6.7	16.1	79.1	4.8	17.09
44	40.1	53.3	6.7	15.5	79.6	4.9	17.91
46	39.6	53.3	7.1	17.7	77.5	4.8	18.72
48	37.9	55.0	7.0	16.7	78.6	4.7	19.54
50	36.0	56.9	7.1	16.6	78.5	4.8	20.35
52	38.4	54.5	7.1	16.7	78.4	4.9	21.16
54	38.3	54.7	6.9	19.4	75.4	5.2	21.98
56	36.4	56.4	7.2	17.0	77.5	5.5	22.79
58	36.3	56.5	7.2	19.7	74.5	5.7	23.61
60	35.9	56.5	7.6	19.3	74.9	5.8	24.42

APPENDIX C

STATISTICAL METHODS

APPENDIX C

STATISTICAL METHODS

I. Series I and II

Intravascular pressures, blood flows, rate of forelimb weight change, and vascular resistances were determined for control periods and during four experimental periods (P_{BA} = 100, 75, 50, and 35 mm Hg) during local hypotension or rapid arterial hemorrhage. For each period, individual means ($\bar{x}$) were calculated for each parameter from three values obtained 1, 3, and 5 minutes after brachial artery pressure stabilized. The individual means were used to calculate a grand mean ($\bar{X}$), variance (S^2), standard deviation (S), and standard error of the mean ($SE_{\bar{X}}$) for each period during clamping or bleeding as follows:

$$\bar{X} = \sum_{i=1}^{n} \frac{\bar{x}_i}{n}$$

$$S^2 = \frac{\sum_{i=1}^{n} \bar{x}_i^2 - \frac{(\sum_{i=1}^{n} \bar{x}_i)^2}{n}}{n-1}$$

$$S = \sqrt{S^2}$$

$$SE_{\bar{X}} = S / \sqrt{n}$$

A. Comparisons of Control Means with Four Experimental Means During Local Hypotension or Hemorrhage

Since a control period preceded the experimental maneuvers (reducing forelimb perfusion pressure by clamping or bleeding), each animal served as its own control and comparisons were made between the control mean and each of the four experimental means (P_{BA} = 100, 75, 50, and 35 mm Hg). If c independent comparisons among means are made, the probability of obtaining at least one significant comparison by chance is $1 - (1 - \alpha)^c$ (where α = error rate for each comparison) (83). Therefore, as the number of comparisons increases, the probability of finding at least one spuriously significant result also increases. Dunnett (43,44) has described a procedure for comparing a control mean with several experimental means in which the probability of making a type I error (α) for the collection of comparisons can be set at a desired level. Dunnett's procedure was used in the present study to determine whether clamping or bleeding to brachial artery pressures of 100, 75, 50, or 35 mm Hg produced significant changes in vascular resistances, mean intraluminal pressures, and rate of forelimb weight change. To eliminate extraneous variance existing among animals, variances of the differences between control and experimental means were used in the test statistic. The test statistic (t_s) for each comparison was:

$$t_s = \frac{\bar{d}}{s_d / \sqrt{n}}$$

where:

$\bar{d}$ = mean difference between the control and experimental values (i.e., mean clamp control resistance minus mean resistance at P_{BA} = 100 mm Hg)

S_d = standard deviation of the difference between the control and experimental mean

n = number of observations

The test statistic was compared with critical values (t_D, 0.05, k, ν) from a Dunnett's t distribution table for 2 sided comparisons based on k experimental periods and ν degrees of freedom (n-1). When variances of the control and experimental means were markedly different, the critical values were modified as:

$$MCV = t_{D,0.05,k,\nu} \left[\frac{1 + f_{0.05,k,\nu} \left(1 - \frac{Se^2}{S_e^2} \right)}{100} \right]$$

where:

MCV = modified critical value

$f_{0.05, k, \nu}$ = adjustment factor from a Dunnett's t distribution table

Sc^2 = variance of control mean

S_e^2 = variance of experimental mean

If t_s exceeded MCV, the null hypothesis ($\mu_{\bar{d}} = 0$) was rejected and the alternative hypothesis ($\mu_{\bar{d}} \neq 0$) was accepted. In this study, a significance level of 0.05 was used for all comparisons.

B. Comparisons of Parameters During Clamping and Bleeding

A standard paired difference test was used to determine whether clamping and bleeding produced significantly different resistances, rate of forelimb weight changes, and mean intraluminal pressures at corresponding brachial artery pressures. The test statistic (t_s) for each comparison was:

$$t_s = \frac{\bar{d}}{S_d / \sqrt{n}}$$

where:

$\bar{d}$ = difference between clamp mean and hemorrhage mean at corresponding brachial artery pressures

S_d = standard deviation of the difference between the clamp and hemorrhage means at a corresponding brachial artery pressure

The test statistic was compared with critical values ($t_{0.05,\nu}$) obtained from a Student's t distribution table. If t_s exceeded $t_{0.05,\nu}$, the null hypothesis ($\mu_{\bar{d}} = 0$) was rejected and the alternative hypothesis ($\mu_{\bar{d}} \neq 0$) was accepted.

C. Comparison of the Resistance Responses of Innervated and Denervated Limbs During Rapid Hemorrhage

To determine whether vascular resistances during rapid hemorrhage were significantly different in innervated (Series I) and denervated (Series II) forelimbs at corresponding brachial artery pressures, a t' statistical test described by Welch (127) for unpaired comparisons was used.

The t' statistic is very accurate in maintaining the desired probability of a type I error over a wide range of sample sizes and does not require that variances of the compared populations be equal (83). The test statistic (t_s) for each comparison was:

$$t_s = \frac{\bar{X}_I - \bar{X}_D}{\sqrt{\frac{S_I^2}{n_I} + \frac{S_D^2}{n_D}}}$$

where:

$\bar{X}_I$ and $\bar{X}_D$ = mean resistance in corresponding vascular segments of innervated and denervated forelimbs at corresponding brachial artery pressures.

S_I^2 and S_D^2 = variances of mean resistances in innervated and denervated forelimbs at corresponding brachial artery pressures.

n_I and n_D = number of observations.

The test statistic was compared with critical values $t'_{0.05, \hat{\nu}}$ obtained from a standard Student's t distribution table based on $\hat{\nu}$ degrees of freedom obtained by Welch's procedure:

$$\hat{\nu} = (1 + g)^2 / [g^2 / (n_I - 1) + 1 / (n_D - 1)]$$

where:

$$g = (S_I^2 / n_I) / (S_D^2 / n_D)$$

For non-integer values of $\hat{\nu}$, the critical values were obtained by interpolation in a Student's t distribution table. If t_s exceeded $t'_{0.05, \hat{\nu}}$, the null hypothesis ($\mu_I = \mu_D$)

was rejected and the alternative hypothesis ($\mu_I \neq \mu_D$) was accepted.

II. Series III

A Mann-Whitney U test was used to determine whether forelimb vascular resistances were significantly different at corresponding brachial artery pressures when the recipient and donor dogs were bled. Since only a small number of experiments (N = 5) were conducted, a non-parametric test was chosen in order to avoid assumptions (required when using parametric methods) about the form of the population distributions. The Mann-Whitney statistic (U or U'), is obtained by ranking the observations from populations A and B, letting the smallest observation have a rank of 1, and using the formulae:

$$U = n_A n_B + \frac{n_A (n_A + 1)}{2} - T_A$$

or

$$U' = n_A n_B + \frac{n_B (n_B + 1)}{2} - T_B$$

where:

T_A = rank sum of population A

T_B = rank sum of population B

n_A = number of observations in population A

n_B = number of observations in population B

Ties in the observations are handled by averaging the ranks that would have been assigned to the tied observations and

assigning the average to each. The test statistic (U or U', whichever is smaller) was used to test the hypothesis that populations A and B are equally distributed. For example, if $n_A = n_B = 5$, and $U = 2$, the hypothesis that populations A and B are equally distributed would be rejected since the probability that $U \leq 2$ is 0.016 (83).

III. Series IV

A. Comparisons Between Control and Experimental Means

To determine whether hemorrhage produced significant changes in vascular resistances, mean systemic arterial pressure, arterial pulse pressure, and central venous pressures in dogs with innervated or denervated forelimbs, Dunnett's t test was used (see Section I-A). Since the probability of rejecting the null hypothesis when it is false (power of a statistical test) decreases as the number of comparisons increases (83), control means were compared with experimental means only at 12, 24, 36, 48, and 60 minutes of bleeding.

B. Comparisons Between Responses of Dogs with Innervated or Denervated Forelimbs

Welch's t' test (see Section I-C) was used to determine whether slow hemorrhage produced significantly different vascular resistance and pressure responses in dogs with innervated or denervated forelimbs. Since vascular

resistances were significantly lower in denervated than innervated forelimbs, resistances were normalized as percent of control before statistical comparison. Means from animals with innervated or denervated forelimbs were compared at 12, 24, 36, 48, and 60 minutes of bleeding.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Abdel-Sayed, W. A., F. M. Abboud, and D. R. Ballard. Contribution of venous resistance to total vascular resistance in skeletal muscle. Am. J. Physiol. 218:1291-1295, 1970.

2. Abboud, F. M. Vascular responses to norepinephrine, angiotensin, vasopressin, and serotonin. Fed. Proc. 27:1391-1395, 1967.

3. Abboud, F. M. Control of various components of the peripheral vasculature. Fed. Proc. 31:1226-1239, 1969.

4. Abboud, F. M. Effects of sodium, angiotensin, and steroids on vascular reactivity in man. Fed. Proc. 33:143-149, 1974.

5. Abboud, F. M. and J. W. Eckstein. Comparative changes in segmental vascular resistances in response to nerve stimulation and to norepinephrine. Circ. Res. 18:263-277, 1966.

6. Adolph, E. F., M. J. Gerbasi, and M. J. Lepore. The rate of entrance of fluid into the blood in hemorrhage. Am. J. Physiol. 104:502-517, 1933.

7. Alexander, R. S. The peripheral venous system. Handbook of Physiology., Circulation 2:1075-1098, 1963.

8. Altura, B. M. Role of glucocorticoids in local regulation of blood flow. Am. J. Physiol. 211:1393-1397, 1966.

9. Altura, B. M. Chemical and humoral regulation of blood flow through the precapillary sphincter. Microvasc. Res. 3:361-384, 1971.

10. Altura, B. M. and S. G. Hershey. Pharmacology of neurohypophyseal hormones and their synthetic analogues in the terminal vascular bed. Angiology 18:428-439, 1967.

11. Angelakos, E. T., M. P. King, and O. C. McKenna. Terminal adrenergic innervation of blood vessels. Circulation 36:Suppl. II, II-53, 1967.

12. Applegren, K. L. Capillary transport in relation to perfusion pressure and capillary flow in hyperemic dog skeletal muscle in shock. Europ. Surg. Res. 4:211-220, 1972.

13. Applegren, K. L. Capillary flow and transport in dog skeletal muscle at prolonged low perfusion pressure. Europ. Surg. Res. 4:221-230, 1972.

14. Applegren, K. L. and D. H. Lewis. Capillary permeability-surface area product (PS) of Renkin in human skeletal muscle. Acta Med. Scand. 184:281-282, 1968.

15. Baker, C. H. Fibrinogen-I^{131}, T-1824, and red cell - Cr^{51} spaces following hemorrhage. Am. J. Physiol. 205:527-532, 1963.

16. Baker, C. H. and J. W. Remington. Fluid shifts after hemorrhage. Am. J. Physiol. 201:910-914, 1961.

17. Barcroft, H. Circulation in skeletal muscle. Handbook of Physiol., Circulation 2:1353-1385, 1963.

18. Beck, L. and A. S. Dontas. Vasomotor activity in hemorrhagic shock. Fed. Proc. 14:318, 1955.

19. Bedford, E. A. The epinephrine content of the blood in conditions of low blood pressure and shock. Am. J. Physiol. 43:235-257, 1917.

20. Bohr, D. F. and B. Johansson. Contraction of vascular smooth muscle in response to plasma: comparison with response to known vasoactive agents. Circ. Res. 19: 593-601, 1966.

21. Bond, R. F., G. F. Lackey, J. A. Taxis, and H. D. Green. Factors governing cutaneous vasoconstriction during hemorrhage. Am. J. Physiol. 219:1210-1215, 1970.

22. Bond, R. F., E. S. Manley, Jr., and H. D. Green. Cutaneous and skeletal muscle vascular responses to hemorrhage. Am. J. Physiol. 212:488-497, 1967.

23. Bronk, D. W. and G. Stella. Afferent impulses in the carotid sinus nerve. J. Cell. Comp. Physiol. 1:113-119, 1932.

24. Brown, J. J., D. L. Davies, A. F. Lever, J. I. S. Robertson, and A. Verniory. The effect of acute hemorrhage in the dog and man on plasma-renin concentrations. J. Physiol. (London) 182:649-663, 1966.

25. Browse, N. L., D. E. Donald, and J. T. Shepherd. Role of the veins in the carotid sinus reflex. Am. J. Physiol. 210:1424-1434, 1966.

26. Browse, N. L., R. R. Lorenz, and J. T. Shepherd. Response of capacity and resistance vessels of dog's limb to sympathetic stimulation. Am. J. Physiol. 210:95-102, 1966.

27. Burton, A. C. Physiology and Biophysics of the Circulation. Year Book Medical Publishers Inc., Chicago, 1965.

28. Carey, L. C. Shock. Proceedings of the Stress Study Group Meeting. Office of Naval Research, Boston, Mass., pp. 129-138, 1972.

29. Celander, O. The range of control exercised by the sympathico-adrenal system. Acta Physiol. Scand. 32:Suppl. 116, 1-132, 1954.

30. Chien, S. Quantitative evaluation of the circulatory adjustment of splenectomized dogs to hemorrhage. Am. J. Physiol. 193:605-614, 1958.

31. Chien, S. Role of the sympathetic nervous system in hemorrhage. Physiol. Rev. 47:214-288, 1967.

32. Claybaugh, J. R. and L. Share. Vasopressin, renin, and cardiovascular responses to continuous slow hemorrhage. Am. J. Physiol. 224:519-523, 1973.

33. Cobbold, A., B. Folkow, I. Kjellmer, and S. Mellander. Nervous and local chemical control of precapillary sphincters in skeletal muscle as measured by changes in filtration coefficient. Acta Physiol. Scand. 57: 180-192, 1963.

34. Corazza, R., L. Manfredia, and F. Raschi. Attivita elettrica delle fibre nervose sympatiche vasomtrici nell' emorragia protratta fino alla morte, nell getto. Minerva Med. 54:1691-1694, 1963.

35. Correll, J. T., L. F. Lythe, S. Long, and J. C. Vanderpole. Some physiological responses to 5-hydroxytryptamine creatine sulfate. Am. J. Physiol. 169:537-544, 1952.

36. Davis, J. O. The control of aldosterone secretion. Physiologist 5:65-86, 1962.

37. Daugherty, R. M., Jr., J. B. Scott, T. E. Emerson, Jr., and F. J. Haddy. Comparison of iv and ia infusion of vasoactive agents on dog forelimb blood flow. Am. J. Physiol. 214:611-619, 1968.

38. Deavers, S., E. L. Smith, and R. A. Huggins. Movement of fluid, albumin and globulins with overtransfusion and hemorrhage. Am. J. Physiol. 205:995-999, 1963.

39. Diana, J. N., R. R. Masden, and J. C. Moore. Peripheral vascular response to vasopressin infusion in the isolated hindlimb of the dog. Fed. Proc. 23:252, 1964.

40. Doberneck, R. C., D. G. Johnson, and R. M. Hardaway. Blood volume adjustment to shock in dogs. Arch. Surg. 86:267-271, 1963.

41. Drees, J. A. and C. F. Rothe. Reflex venoconstriction and capacity vessel pressure-volume relationships in dogs. Circ. Res. 34:360-373, 1974.

42. DuCharme, D. W. and L. Beck. The relative effect of the renal pressor and sympathetic nervous system on vascular capacity during hypotension. J. Pharm. Exp. Therapeut. 177:56-68, 1971.

43. Dunnett, C. W. A multiple comparison procedure for comparing several treatments with a control. J. Am. Statist. Assoc. 50:1096-1121, 1955.

44. Dunnett, C. W. New tables for multiple comparisons with a control. Biometrics 20:482-491, 1962.

45. Euler, U. S. von. Adrenaline and noradrenaline. Distribution and action. Pharmacol. Rev. 6:15-22, 1954.

46. Falck, B. Observations on the possibilities of the cellular localization of monoamines by a fluorescence method. Acta Physiol. Scand. 56:Suppl. 197, 1-25, 1962.

47. Feldberg, W. and G. P. Lewis. The action of peptides on the adrenal medulla. Release of adrenaline by bradykinin and angiotensin. J. Physiol. (London) 171:98-108, 1964.

48. Fell, C. Changes in distribution of blood flow in irreversible hemorrhagic shock. Am. J. Physiol. 210:863-868, 1966.

49. Folkow, B. A critical study of some methods used in investigations on the blood circulation. Acta Physiol. Scand. 27:118-129, 1952.

50. Folkow, B. Nervous control of blood vessels. Physiol. Rev. 35:629-663, 1955.

51. Folkow, B., B. Johansson, and S. Mellander. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections. Acta Physiol. Scand. 53:99-104, 1961.

52. Folkow, B. and S. Mellander. Aspects of the nervous control of the precapillary sphincters with regard to the capillary exchange. Acta Physiol. Scand. 50:Suppl. 175, 52-54, 1960.

53. Folkow, B. and E. Neill. Circulation. Oxford Univ. Press, London, 1971.

54. Folkow, B. and B. Öberg. Autoregulation and basal tone in consecutive vascular sections of the skeletal muscles of reserpine-treated cats. Acta Physiol. Scand. 53: 105-113, 1961.

55. Forsyth, R. P., B. I. Hoffbrand, and K. L. Melmon. Redistribution of cardiac output during hemorrhage in the unanesthetized monkey. Circ. Res. 27:311-319, 1970.

56. Fowler, N. O., R. Shabetai, and J. C. Holmes. Adrenal medullary secretion during hyposia, bleeding, and rapid intravenous infusion. Circ. Res. 9:427-435, 1961.

57. Frank, H. A., E. D. Frank, H. Korman, I. A. Macchi, and O. Hechter. Corticosteroid output and adrenal blood flow during hemorrhagic shock in dogs. Am. J. Physiol. 182:24-28, 1955.

58. Fuxe, K. and G. Sedvall. The distribution of adrenergic nerve fibers to the blood vessels in skeletal muscle. Acta Physiol. Scand. 64:75-86, 1965.

59. Gauer, O. H. and J. P. Henry. Circulatory basis of fluid volume control. Physiol. Rev. 43:423-481, 1963.

60. Gauer, O. H., J. P. Henry, and C. Behn. The regulation of extracellular fluid volume. Ann. Rev. Physiol. 32: 547-595, 1970.

61. Gernandt, B., G. Liljestrand, and Y. Zotterman. Efferent impulses in the splanchnic nerve. Acta Physiol. Scand. 11:231-247, 1946.

62. Gonzalez, R. R., Jr. and R. F. Bond. Sympathetic nerve and skeletal muscle vascular responses to hemorrhage and shock, with and without cholinergic and β-adrenergic blockage in the dog. Circulatory Shock 1:39-50, 1974.

63. Green, H. D. Physiology of the peripheral circulation in shock. Fed. Proc. 20:Suppl. 9, 61-68, 1961.

64. Grega, G. J. and F. J. Haddy. Forelimb transcapillary fluid fluxes and vascular resistances in catecholamine shock. Am. J. Physiol. 220:1448-1462, 1971.

65. Grega, G. J., J. M. Schwinghamer, and F. J. Haddy. Effects of hemorrhagic and catecholamine shock on canine transcapillary fluid fluxes and segmental vascular resistances. Shock: Biochemical, Pharmacological and Chemical Aspects. Ed. A. Bertelli and N. Black. Plenum Press, New York, pp. 3-14, 1970.

66. Grega, G. J., J. M. Schwinghamer, and F. J. Haddy. Changes in forelimb weight and segmental vascular resistances following severe hemorrhage. Circ. Res. 29:691-703, 1971.

67. Gregerson, M. I. and R. A. Rawson. Blood volume. Physiol. Rev. 39:307-342, 1954.

68. Groom, A. C., S. Rowlands, and H. W. Thomas. Some circulatory responses to hemorrhage in the cat: a critical level of blood volume for the onset of hypotension. Quart. J. Exptl. Physiol. 50:385-405, 1965.

69. Guyton, A. C. Circulatory Physiology: Cardiac Output and its Regulation. W. B. Saunders Co., Philadelphia, 1963.

70. Haddy, F. J., J. I. Molnar, C. W. Borden, and E. C. Texter. Comparison of direct effects of angiotensin and other vasoactive agents on small and large blood vessels in several vascular beds. Circulation 25: 239-246, 1962.

71. Haddy, F. J., J. I. Molnar, and R. W. Campbell. Effects of denervation and vasoactive agents on vascular pressures and weight of dog forelimb. Am. J. Physiol. 201:631-638, 1961.

72. Haddy, F. J., H. W. Overbeck, and R. M. Daugherty, Jr. Peripheral vascular resistance. Ann. Rev. Med. 19: 167-194, 1968.

73. Haddy, F. J. and J. B. Scott. Cardiovascular Pharmacology. Ann. Rev. Pharmacol. 6:49-76, 1966.

74. Haddy, F. J. and J. B. Scott. Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol. Rev. 48:688-707, 1968.

75. Haddy, F. J., J. B. Scott, and J. I. Molnar. Mechanism of volume replacement and vascular constriction following hemorrhage. Am. J. Physiol. 208:169-181, 1961.

76. Hall, J., B. Lalone, and J. Schwinghamer. Mechanism of large vessel constriction and fluid mobilization during hemorrhage. Physiologist 15:158, 1972.

77. Hall, R. C. and R. L. Hodge. Changes in catecholamine and angiotensin levels in the cat and dog during hemorrhage. Am. J. Physiol. 221:1305-1309, 1971.

78. Hammond, M. C., D. L. Davis, and P. Dow. Segmental responses of dog paw vasculature. Circ. Res. 23:1-9, 1968.

79. Healy, J. K. Effect of intravenous angiotensin infusion on adrenal medullary function in man. Proc. Soc. Exptl. Biol. and Med. 125:679, 1967.

80. Järhult, J. Osmotic fluid transfer from tissue to blood during hemorrhagic hypotension. Acta Physiol. Scand. 89:213-226, 1973.

81. Järhult, J., J. Lundvall, S. Mellander, and S. Tibblin. Osmolar control of plasma volume during hemorrhagic hypotension. Acta Physiol. Scand. 85:142-144, 1972.

82. Johnson, P. C., K. M. Hanson, and O. Thulesius. Pre- and postcapillary resistance in the dog forelimb. Am. J. Physiol. 210:873-876, 1966.

83. Kirk, R. E. Experimental Design: Procedures for the Behavioral Sciences. Wadsworth Publishing Co., Belmont, Calif., 1968.

84. Landis, E. M. Micro-injection studies of capillary permeability. Am. J. Physiol. 82:217-238, 1937.

85. Landis, E. M. and J. R. Pappenheimer. Exchange of substances through the capillary walls. Handbook of Physiol., Circulation 2:961-1034, 1963.

86. Lassen, N. A. and J. Trap-Jensen. Theoretical considerations of measurement of capillary diffusion capacity in skeletal muscle by the local clearance method. Scand. J. Clin. Lab. Invest. 21:116-122, 1968.

87. Lesh, T. A. and C. F. Rothe. Sympathetic and hemodynamic effects on capacitance vessels in dog skeletal muscle. Am. J. Physiol. 217:819-827, 1969.

88. Lister, J., I. F. McNeill, V. C. Marshall, L. F. Plzak, F. J. Dagher, and F. D. Moore. Transcapillary refilling after hemorrhage in normal man: basal rates and volumes. Effect of norepinephrine. Ann. Surg. 158: 698-712, 1963.

89. Lundgren, O., J. Lundvall, and S. Mellander. Range of sympathetic discharge and reflex vascular adjustments in skeletal muscle during hemorrhagic hypotension. Acta Physiol. Scand. 62:380-390, 1964.

90. McNeill, I. F., J. P. Dixon, and F. D. Moore. The effects of hemorrhage and hormones on the partition of body water. II. The effects of acute single and multiple hemorrhage and adrenal corticoids in the dog. J. Surg. Res. 3:332-343, 1963.

91. McNeill, J. R., R. D. Stark, and C. V. Greenway. Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. Am. J. Physiol. 219: 1342-1347, 1970.

92. Mellander, S. Comparative studies on the adrenergic neuro-humoral control of resistance and capacitance vessels in the cat. Acta Physiol. Scand. 50:Suppl. 176, 1-86, 1960.

93. Mellander, S. Contributions of small vessel tone to the regulation of blood volume and formation of oedema. Proc. Royal Soc. Med. 61:51-61 (section on experimental medicine and therapeutics, pp. 1-7), 1968.

94. Mellander, S. Systemic circulation: local control. Ann. Rev. Physiol. 32:313-344, 1970.

95. Mellander, S. and B. Johansson. Control of resistance, exchange, and capacitance functions in the peripheral circulation. Pharmacol. Rev. 20:117-196, 1968.

96. Mellander, S. and D. H. Lewis. Effect of hemorrhagic shock on the reactivity of resistance and capacitance vessels and on capillary filtration transfer in cat skeletal muscle. Circ. Res. 13:105-118, 1963.

97. Miller, M. E. Guide to the Dissection of the Dog, 3rd ed., Edwards Brothers Inc., Ann Arbor, Mich., pp. 160-167, 1962.

98. Öberg, B. Effects of cardiovascular reflexes on net transcapillary fluid transfer. Acta Physiol. Scand. 62:Suppl. 229, 1-98, 1964.

99. Öberg, B. The relationship between active constriction and passive recoil of the veins at various distending pressures. Acta Physiol. Scand. 71:223-247, 1967.

100. Öberg, P. A. and U. Sjöstrand. Studies of blood-pressure regulation. II. On-line simulation as a method of studying the regulatory properties of the carotid-sinus reflex. Acta Physiol. Scand. 75:287-300, 1969.

101. Pappenheimer, J. R. and A. Soto-Rivera. Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. Am. J. Physiol. 152:471-491, 1948.

102. Pareira, M., E. Serkes, and S. Lang. Plasma volume response to graded hemorrhage. Surgery 52:378-381, 1962.

103. Powell, J. R. and D. W. DuCharme. Effect of renal pressor systems on vascular capacity during hemorrhage. Am. J. Physiol. 226:168-172, 1974.

104. Renkin, E. M. Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles. Am. J. Physiol. 197:1205-1210, 1959.

105. Renkin, E. M. and S. Rosell. The influence of sympathetic adrenergic vasoconstrictor nerves on transport of diffusible solute from blood to tissues in skeletal muscle. Acta Physiol. Scand. 54:223-240, 1962.

106. Renkin, E. M. and R. M. Sheehan. Uptake of ^{42}K and ^{86}Rb in skeletal muscle from continuous arterial infusion. Capillary Permeability: Proceedings of the Alfred Benzon Symposium II, Ed. C Crone and N. A. Lassen, Munksgaard, Copenhagen, pp. 310-318, 1969.

107. Rocka e Silva, M., Jr. and M. Rosenberg. The release of vasopressin in response to hemorrhage and its role in the mechanism of blood pressure regulation. J. Physiol. (London) 202:535-557, 1969.

108. Rothe, C. F. Heart failure and fluid loss in hemorrhagic shock. Fed. Proc. 29:1854-1860, 1970.

109. Rothe, C. F., F. C. Schwendenmann, and E. E. Selkurt. Neurogenic control of skeletal muscle resistance in hemorrhagic shock. Am. J. Physiol. 204:925-932, 1962.

110. Rothe, C. F. and E. E. Selkurt. Cardiac and peripheral failure in hemorrhagic shock in the dog. Am. J. Physiol. 207:203-214, 1964.

111. Scher, A. M. and A. C. Young. Servoanalysis of carotid sinus reflex effects on peripheral resistance. Circ. Res. 12:152-162, 1966.

112. Schmid, P. G., F. M. Abboud, M. G. Wendling, E. S. Ramberg, A. L. Mark, D. D. Heistad, and J. W. Eckstein. Regional vascular effects of vasopressin: plasma levels and circulatory responses. Am. J. Physiol. (In press)

113. Schmid, P. G., J. W. Eckstein, and F. M. Abboud. Effect of 9 α-fluorohydrocortisone on forearm vascular responses to norepinephrine. Circulation 34:620-626, 1966.

114. Schmid, P. G., J. W. Eckstein, and F. M. Abboud. Effect of 9 α-fluorohydrocortisone on forearm venous responses to norepinephrine and tyramine. J. Appl. Physiol. 23:571-574, 1967.

115. Schwinghamer, J. M., G. J. Grega, and F. J. Haddy. Skin and muscle circulatory responses during prolonged hypovolemia. Am. J. Physiol. 219:318-326, 1970.

116. Scott, J. B., R. M. Daugherty, and F. J. Haddy. Effect of severe local hypoxemia on transcapillary water movement in dog forelimb. Am. J. Physiol. 212:847-851, 1967.

117. Selhurt, E. E. Renal blood flow and renal clearance during hemorrhagic shock. Am. J. Physiol. 145:699-709, 1966.

118. Shadle, O. W., M. Zukof, and J. Diana. Translocation of blood in the isolated dog's hindlimb during levarterenol infusion and sciatic nerve stimulation. Circ. Res. 6:326-333, 1958.

119. Share, L. and J. R. Claybaugh. Regulation of body fluids. Ann. Rev. Physiol. 34:235-260, 1972.

120. Sjöstrand, T. Blood Volume. Handbook of Physiol., Circulation 2:51-62, 1963.

121. Skelton, H. The storage of water by various tissues of the body. Arch. Intern. Med. 40:140-152, 1927.

122. Smith, E. L., R. A. Huggins, and S. Deavers. Effect of blood volume on movement of protein and volume distribution of albumin in the dog. Am. J. Vet. Res. 26:829-836, 1965.

123. Starling, E. H. On the absorption of fluids from the connective tissue spaces. J. Physiol. (London) 19: 312-326, 1896.

124. Walker, W. F., M. S. Zileli, F. W. Reutter, W. C. Shoemaker, D. Friend, and F. D. Moore. Adrenal medullary secretion in hemorrhagic shock. Am. J. Physiol. 197:773-780, 1959.

125. Watts, D. T. Adrenergic mechanisms in hypovolemia and shock. Shock and Hypotension. Ed. L. C. Mills and J. H. Moyer. Grune and Stratton, New York, pp. 385-391, 1965.

126. Watts, D. T. and V. Wertfall. Studies on peripheral blood catecholamine levels during hemorrhagic shock in dogs. Proc. Soc. Exptl. Biol. Med. 115:601-604, 1964.

127. Welch, B. L. The generalization of Student's problem when several different population variances are involved. Biometrika 34:28-35, 1947.

128. Weideman, M. P. Dimensions of blood vessels from distributing artery to collecting vein. Circ. Res. 12:375-378, 1963.

129. Zimmerman, B. G. Effect of acute sympathectomy on responses to angiotensin and norepinephrine. Circ. Res. 11:780-787, 1962.

130. Zimmerman, B. G. Separation of responses of arteries and veins to sympathetic stimulation. Circ. Res. 18: 429-436, 1966.

131. Zimmerman, B. G. Drug action on peripheral vascular system. Ann. Rev. Pharmacol. 12:125-140, 1972.